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OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK, FINLAND, NORWAY AND SWEDEN

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# ARMAMENTARIUM FOR RADIUM TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

by

O KJELLGREN and I RAGNHULT

Several different types of radium applicators have been developed since the radium treatment of carcinoma of the uterine cervix has become the method of choice Radium therapy was previously extensively employed but since the introduction of the supervoltage therapy its use in primary treatment has become less general It is however still considered the best primary method of dealing with most cases of cancer of the uterine cervix

All means of applying radium in the treatment of carcinoma of the cervix of the uterus have derived from one of two fundamental methods the Paris or the Stockholm method Several of the current local radiation procedures in this condition are illustrated in Fig 1

The Paris method, a protracted low intensity technique of radium treatment was devised in the beginning of the nineteen twenties by REGAUD et coll at the Radium Institute, Paris It makes use of small quantities of radium applied for the fairly long time of about 5 days the total dose amounting to about 8 000 mgh

The Manchester method was developed from the Paris method, the main feature is the delivery of a predetermined dose to arbitrarily defined points in the pelvis independently of the arrangement of the applicators, it entails

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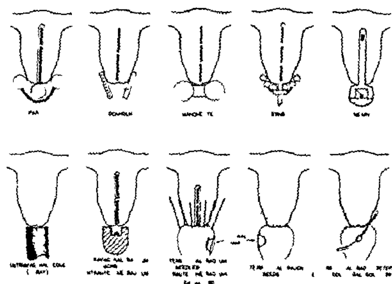


Fig 1 After GRAHAM 1937

differential loading of the applicators dependent upon their size and length The optimal dose at point A defined as 2 cm lateral to the uterine canal and 2 cm above the vaginal fornix has been determined as 7 500 to 8 000 r in two treatments given with an interval of one week (TOD 1941, TOD & MEREDITH 1938)

The Stockholm method was originally devised by FORSSELL & HEYMAN and has been further developed by KOTTMEIER at Radiumhemmet The technique is based on repeated treatments with fairly large amounts of radium for a relatively short time a number of different applicators being used Advantage is taken of the possibilities of selecting the treatment with due regard to the type of the tumour and its spread the patient s general condition and so on The length of the intrauterine applicators depends on the length of the uterus The applicators as a rule are permanently loaded contain from 53 to 88 mg radium and are so designed that the dose rate 2 cm from the center of the applicator is about 75 r/h The vaginal applicators most of which are also permanently loaded vary in shape and size and mostly contain 60 to 80 mg radium the radium is usually spread towards the lateral parts of the boxes The time of treatment generally amounts to about 27 hours at each of two sittings 3 weeks apart The total filtration is equivalent to 2 to 3 mm of lead The dose at the bladder and the rectum is checked by dose measurements, making it possible to avoid overdosage in these organs by cutting down the treatment time when the dose rate is too high The optimal total dose to the rectum from the radium is 4 000 r and to the bladder about 5 500 r These doses are generally not exceeded in early stages of carcinoma of the cervix

but up to 6 000 r may be given to the rectum in advanced stages (KOTTMEIER 1959)

The dose from the intrauterine applicator may be raised by increasing the time of treatment or the amount of radium The diameter of the applicator is increased to 13 mm from the usual 7 mm in these cases, in order to avoid an excessive dose to the uterine wall Experience has shown that dilatation of the cervical canal to Hegar 13 may generally be made without difficulty A higher intrauterine dose is usually given in cases of endocervical carcinoma, paracervical growth, palpable metastases at the pelvic wall, or in cases with a narrow vagina The vaginal dose must then be correspondingly decreased Three weeks after the second application, roentgen or telecobalt treatment towards the parametria and pelvic walls is generally administered by the split field technique with two anterior and two posterior portals Primary roentgen or telecobalt treatment through one large anterior portal, and one or two posterior portals, is given only in advanced cases or in cases with large cauliflower tumours Perineal portals may also be used in the latter condition

The dose administered to the cervix amounts to about 20 000 r but much less is received by the pelvic walls Provided the intrauterine radium is not applied as far down as the external os the dose at point A with the current Stockholm method amounts to about 6 000 r With the radium at the external os, the dose to the cervix at the rectum, and at point A increases, however The dose on the pelvic walls from the intracavitary radium amounts to between 610 and 2 430 r, provided the uterus is situated in the center of the pelvis The obturator nerve receives about 1 335 r, 60 to 70 % of which is from the intrauterine radium (KOTTMEIER 1953)

Detailed studies of the dose distribution in the pelvis with the Stockholm method have been made by KOTTMEIER (1951 and 1953) and WALSTAM (1954)

A number of special applicators for radium treatment of carcinoma of the cervix have been described and include Ernst s applicator, Neary s applicator, and the Buffalo applicator used at Roswell Park Memorial Institute Interstitial radium needles in the tumour combined with intrauterine radium or $Co^{60}$, an intravaginal radium bomb combined with intrauterine radium or intravaginal roentgen irradiation through a vaginal cone are other methods of local radiologic treatment (For references see GRAHAM et coll 1962 )

It is of great importance to be familiar with the method used and to be aware of the dose delivered to the different parts of the tumour and the pelvic organs regardless of which method is being used

## Armamentarium

A system of permanently loaded applicators for the radium treatment of carcinoma of the uterine cervix have been developed during recent years in our department, the applicators being similar to those used in the Stockholm

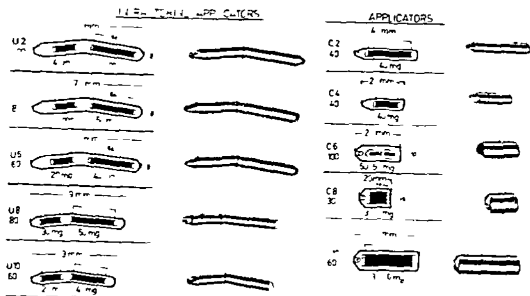



Fig 2

method The dose rate in r h at a point 2 cm from the center of the intrauterine applicators is however not constant but numerically equal to the radium content in mg

Primary radium treatment of carcinoma of the cervix with this armamentarium is generally given in three applications 13 to 14 days apart The interval is adjusted so that the second and third treatment will be administered at the time when the radiation reaction in the vaginal smear from the preceeding treatment has reached its peak (KJELLGREN 1958) If the tumour is confined to the portio or the vagina the first two treatments usually consist of combined intrauterine and vaginal applications and the third only a vaginal application An intrauterine application is given at the third treatment if the tumour is of endocervical origin or has a large paracervical spread

Five different intrauterine applicators (U2 U4 U6 U8 and U10) are used These are permanently loaded with 60 80 or 100 mg radium and vary in length from 53 to 70 mm The applicators C2 and C4 each containing 40 mg radium are used for applications in cervical stumps One applicator (C6), containing 100 mg radium and one small (C8) and one large (C10) cylindrical applicators, containing 30 mg and 60 mg of radium respectively are used for applications to craters The intrauterine applicators U2 to U10 with a bent knee of 13 and the applicators C2 to C10 are made of stainless steel The corporal part contains a larger quantity of radium than the cervical part The length of the applicators the diameter, the amount of radium and the active length are given in Fig 2 Attention should be paid to the fact that the radium in the cervical part of the applicator does not reach to the lower end

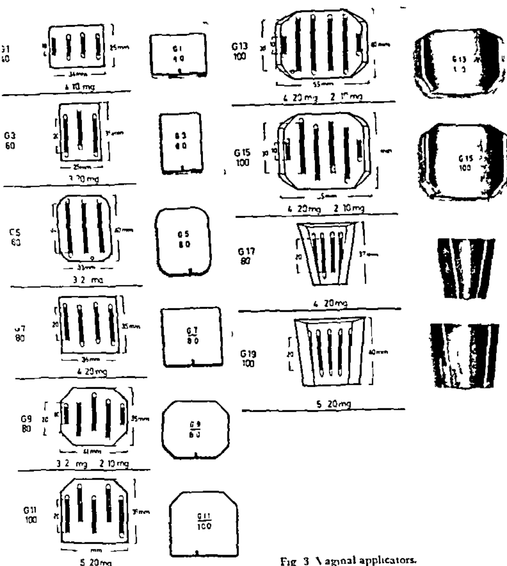
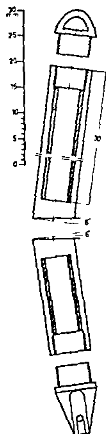


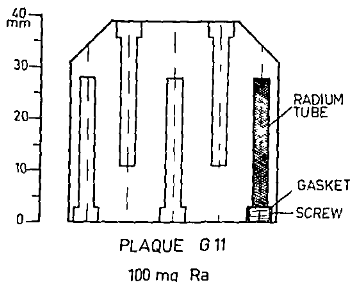
Fig 3 Vaginal applicators.

which means that with the applicator pushed up to the fundus no radium is contained in 1 5 to 2 cm of the lower part of the cervix The isodose curves do not therefore surround the applicators symmetrically but are displaced more towards the corporal end (Figs 6 to 15)

Six flat (G1, G3 G5 G7, G9 and G11) and four curved plaques (G13 G15 G17 and G19) are used for vaginal applications Some have cut-off corners in order to fit into the vaginal fornices The two plaques G13 and G15 are slightly curved in order to accommodate large tumours or a large bulky portio of a wide vagina The curved plaques G17 and G19 are segments of the surface of



INTRAUTERINE APPLICATOR U2
100mg Ra




Figs 4 and 5 Constructional details of an intrauterine and a vaginal applicator

a truncated cone and are designed to cover tumours growing down into the vagina The plaques are loaded with 40, 60 80 or 100 mg of radium

The vaginal plaques with the exception of G17 and G19 are manufactured from stainless steel and have a thickness of 8 mm The other dimensions are given in Fig 3 Plaques G17 and G19 are made of Monel metal The radium tubes are inserted in drilled holes and sealed off by 0 5 mm rubber gaskets and stainless steel screws

The total filtering equivalent of both the intrauterine and the vaginal applicators is 3 mm Pb Constructional details of an intrauterine and a vaginal applicator are presented in Figs 4 and 5

### Measurement of the dose distribution around the applicators

The isodose curves for the intrauterine and vaginal applicators were measured in a water phantom with a scintillation detector, fitted with a small anthracene

crystal 3 mm in diameter, and mounted in a long well polished aluminium tube to serve as light pipe between the crystal and the photo-cathode The scintillation detector was moved along the isodose curves by means of an automatic isodose plotter developed by LARSSON et coll The movements of the detector were reproduced by a pen that drew the isodose curves on paper

The isodose distribution was measured in four different planes for all the vaginal plaques, excepting G13 and G15 which were measured in three planes only The intrauterine applicators were measured in two planes and the small straight applicators in only one plane The measuring planes were chosen to facilitate clinical evaluation of the dose distribution in the uterus, vagina and the tumour, plane m gives the dose rate 2 mm from the applicator, plane n the dose rate 2 cm above the plane of the radium tubes, and planes k and l give the dose distributions in the frontal and the sagittal planes respectively (cf Fig 21)

The diagrams indicate that the different intrauterine applicators give about 1 000 r per 1 000 mgh at a distance of 2 cm from the center of the applicators The different vaginal plaques produce about 1 200 to 1 300 r per 1 000 mgh 2 cm above the surface

All these applicators are readily sterilized and being permanently loaded need little handling which reduces the total radiation hazards Dose estimations may be made by means of isodose diagrams which are available in standardized planes around the applicators A system of preloaded applicators with a fixed radium distribution somewhat decreases the possibility of modifying any one treatment

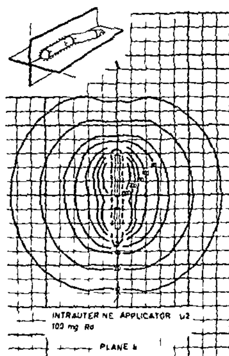



Fig 6

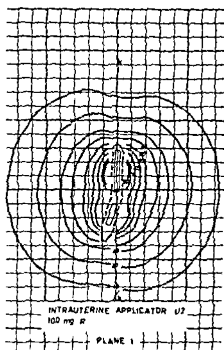



Fig 7

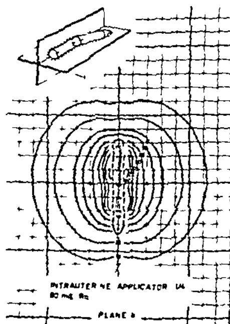



Fig 8

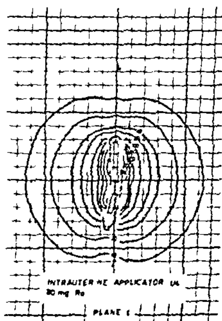



Fig 9

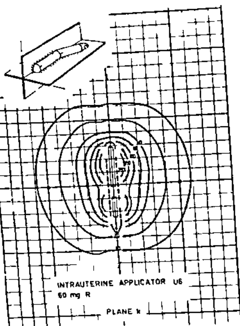



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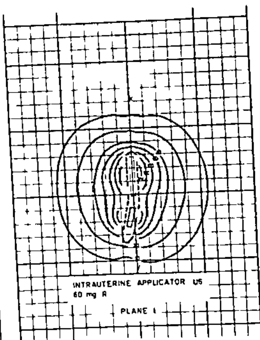



Fig 11

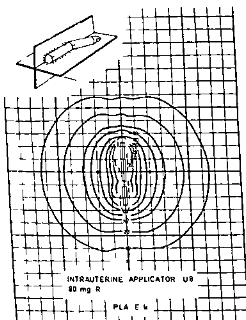



Fig 12

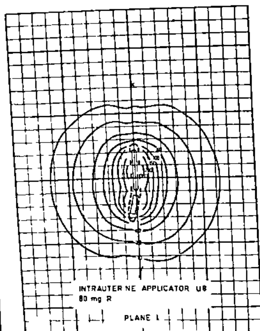



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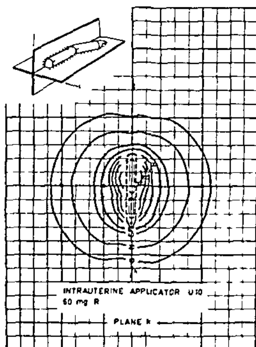



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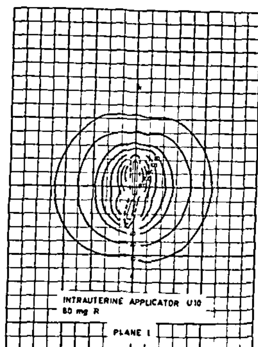



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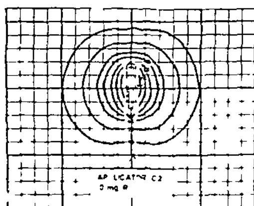


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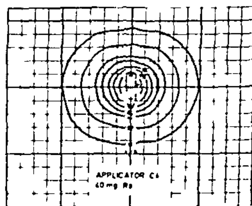



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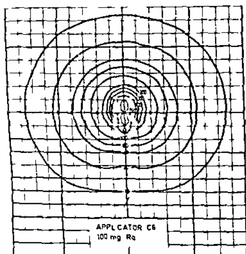



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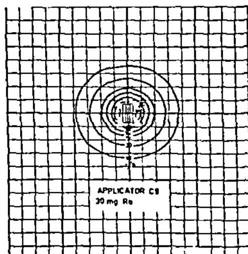



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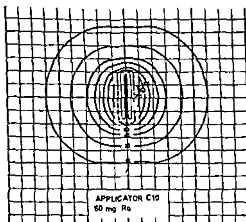



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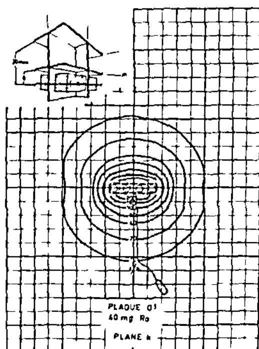



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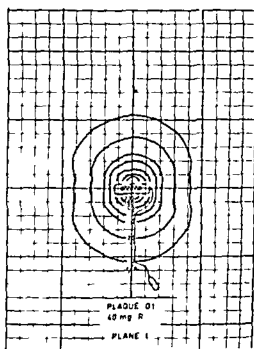



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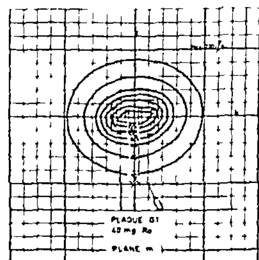



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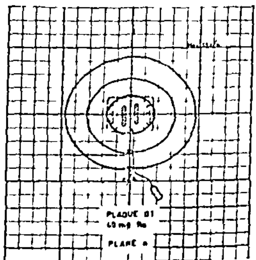



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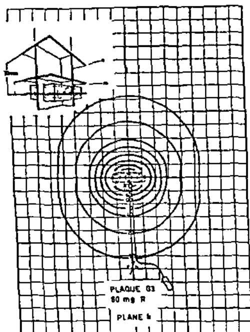



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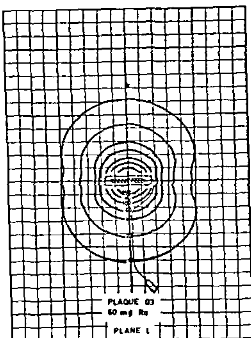



Fig 26

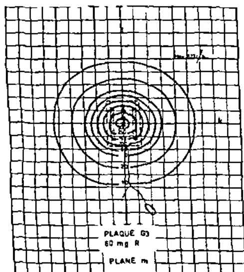



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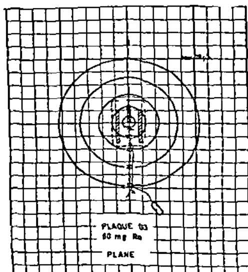



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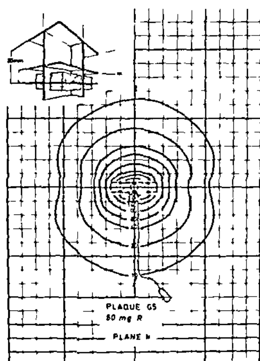



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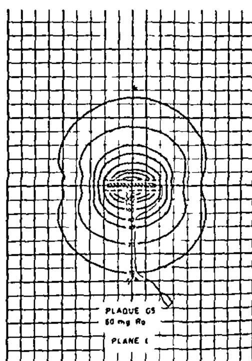



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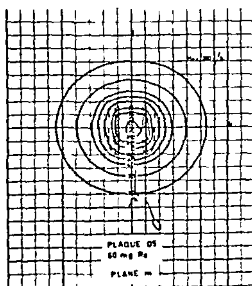



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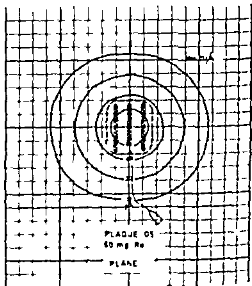



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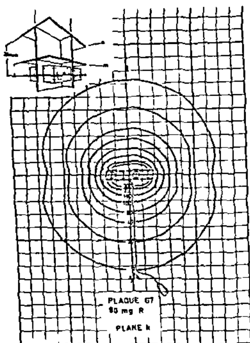



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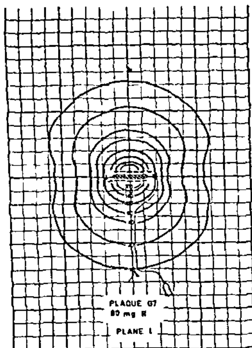



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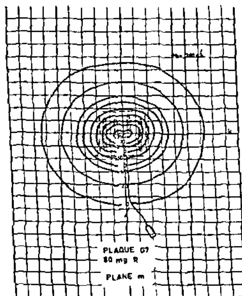



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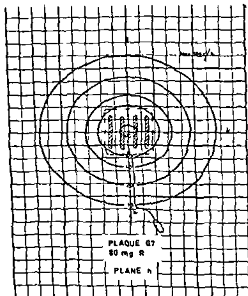



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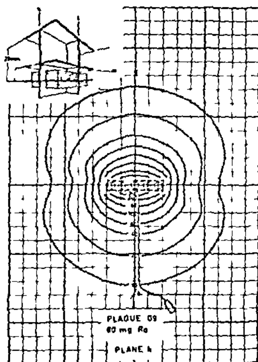



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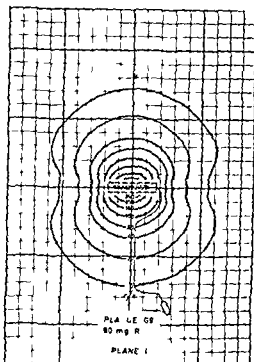



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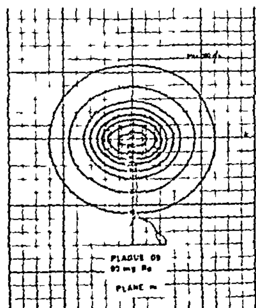



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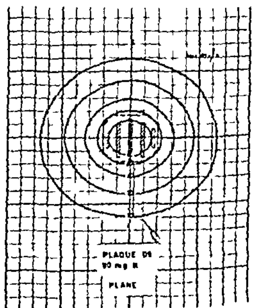



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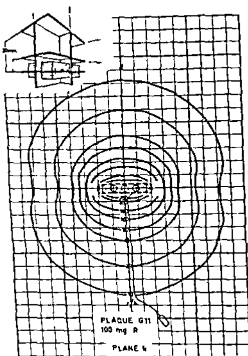



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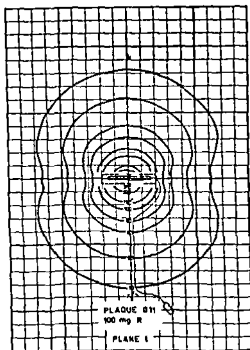



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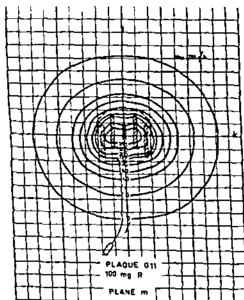



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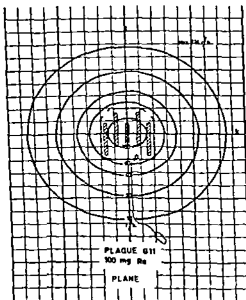



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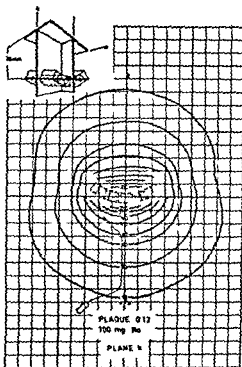



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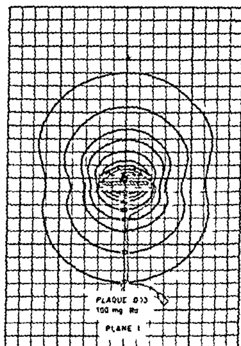



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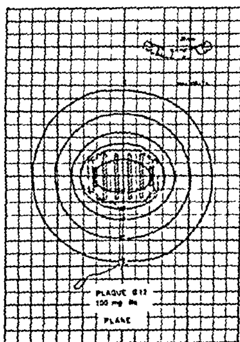



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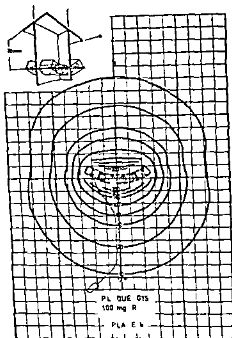



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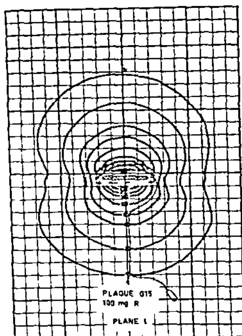



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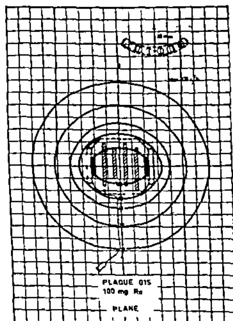



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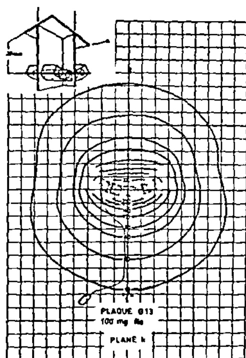



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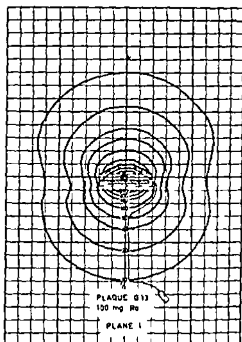



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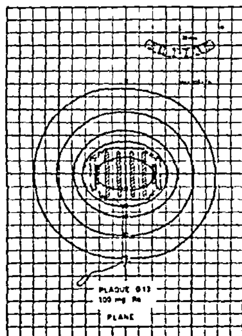



Fig 47

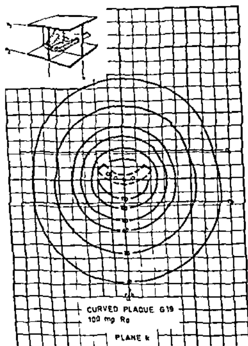



*Fig* 55

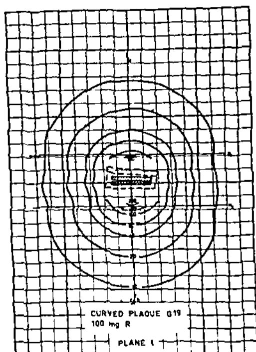



*Fig* 56

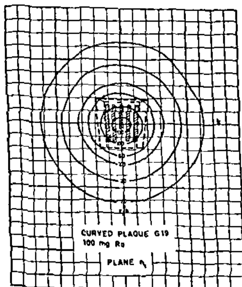



Fig 57

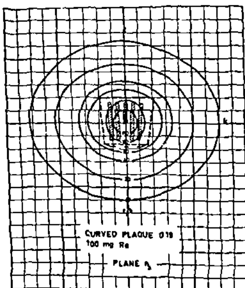



Fig 58

## SUMMARY

A system of permanently loaded applicators for the treatment of carcinoma of the cervix of the uterus is described Isodose curves in different planes around the applicators are presented

## ZUSAMMENFASSUNG

Ein System von dauernd geladenen Radiumeinlagen zur Behandlung des Cervixkarzinoms wird beschrieben Die Arbeit enthalt die nötigen Isodosenkurven in verschiedenen Ebenen

## RÉSUMÉ

Les auteurs décrivent un système d applicateurs chargés en permanence pour la curie thérapie du cancer du col de l utérus Ils présentent les courbes isodoses dans différents plans autour des applicateurs


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FROM THE UROLOGIC SECTION (DIRECTOR ANDREAS PALMLOV) OF THE DEPARTMENT OF SURGERY ST ERIK'S SJUKHUS, AND THE ISOTOPE LABORATORY (DIRECTOR ERIK ODEBLAD), THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY AT SABBATSBERG S SJUKHUS STOCKHOLM SWEDEN

# AUTORADIOGRAPHIC STUDIES OF THE TESTIS AND THE EPIDIDYMIS IN MAN AFTER INCUBATION WITH RADIOACTIVE ZINC IN VITRO

by

KARL EKBOM and BENGT WETTERDAL

The spermatozoa in man have been found to have a particularly high content of zinc compared to other tissues (MAWSON & FISCHER 1953 and BIRNBAUM HALL & LEE 1961) Very little however seems to be known about the localization of zinc in the male reproductive organs and of this physiologic importance The present investigations on the distribution of zinc in the testis and in the epididymis were carried out in an attempt to gain further information concerning this matter

Autoradiographic studie on the testes in rats by WETTERDAL (1958) demonstrated that the $^{65}$Zn administered was concentrated in the seminiferous *tubules* Scintillation measurements and autoradiography further indicated *that the* spermatozoa took up the isotope in the seminiferous tubules and *with a* high amount of $^{65}$Zn were transported through the sperm transport system to the ejaculate

MILLAR, ELCOATE FISCHER & MAWSON (1960) suggested that the incorporation of large amounts of zinc in the spermatozoa is essential for their *development* and for the maintenance of the germinal epithelium

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MILLAR, VINCENT & MAWSON (1961) studied the localization of $^{65}$Zn in different rat tissues by autoradiography and suggested that it is slowly incorporated into the spermatozoa during their development in the testes They found like WETTERDAL, that the spermatozoa progressed from the testes through the epididymal ducts with the radioactive zinc

DANIEL, HADDAD, PROUT & WHITMORE (1956) and PROUT SIERP & WHITMORE (1959) injected $^{65}$Zn intravenously in human subjects suffering from various urologic disorders The amount of $^{65}$Zn in the different organs and tissues removed was studied by scintillation measurements DANIEL et coll (1956) were able to produce an autoradiograph of a prostatic adenoma no autoradiographs of the testes and the epididymes were obtained, however

$^{65}$Zn seems at present to be the only radioactive zinc isotope readily available for experimental studies Autoradiographic detection of $^{65}$Zn is however, rather difficult because of the small amount (1 6 %) of beta rays in the decay scheme This fact and the relatively long half life of 244 days of $^{65}$Zn make this isotope less suitable for autoradiographic studies in vivo in man

TAYLOR (1957) reported that slices of tissues incubated with $^{65}$Zn in vitro will take up the isotope in concentrations corresponding to those obtained after its injection into the intact animal This in vitro technique appeared to be a suitable one with which to study the localization of $^{65}$Zn incubated in the testes and epididymes in man

*Material and Methods* The testes and the epididymes were obtained from three patients subjected to unilateral or bilateral removal of the scrotal contents

The unilateral operation was carried out on a 68 year old man with a recurrent scrotal hydrocele and on whom hydrocelectomy had earlier been performed The bilateral operations were performed on two elderly men, aged 72 and 78, with carcinoma of the prostate Both subjects had been treated with an oestrogen, aethinyloestradiolum, 0 15 mg daily The first man received oestrogen at short intervals over 9 months, about a year later operation was undertaken because the patient refused to continue the oestrogen treatment regularly The 78-year-old man received oestrogen for only two weeks when the therapy had to be abandoned because of allergic reactions, operation was performed 4 months later The two subjects were in good general condition without clinical and roentgenologic signs of metastases

The original radioactive zinc, $^{65}$Zn, was obtained from the Biochemical Centre, Amersham, England, as a $^{65}$Zn $Cl_2$ solution The original isotope solution was diluted with 0 85 % sodium chloride to a final solution of 40 $\mu$C/ml specific activity and a pH of 6 5 in which the organs to be studied were immersed

Small 4 to 8 mm cubes were cut out from the testes and the epididymes and incubated in the radioactive solution for two hours at + 37 C The tissues were fixed in formalin and processed by standard methods, 5 to 8 $\mu$ serial

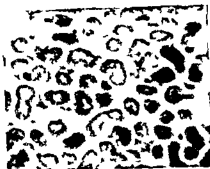


Fig 1 Autoradiograph from the testis of a 68 year-old man after incubation with Zn in vitro Blackened areas indicate high concentrations of radioactivity × 30

sections were cut and every second one was mounted on glass and the others on methacrylate slides, the former being stained with hematoxylin and eosin

The methacrylate slides were subjected to autoradiography Agfa Printon Rapid films were used and the apposition technique and the exposure of the films were carried out in accordance with the method described by ODEBLAD (1952) An appropriate blackening of the films was obtained after an exposure time of 4 months The films were developed in Gaevert 209 A at 20 to 22° C and fixed in Gaevert Acido Fix

## Results

Autoradiographs of the testis and of the epididymis are presented in Figs 1 and 2 The concentration of $^{65}$Zn is indicated by blackening in the reproductions

The concentration of radioactive zinc showed a characteristic and uniform pattern with a various degree of uptake in the different tissue elements in all the areas examined The peripheral parts of the tissues presented no visible increase in radioactivity compared to the central parts

The germinal cells in the testes and the epithelium cells lining the epididymal ducts showed evidence of a relatively high concentration of radioactive zinc compared to the interstitial tissues in these areas The contents of the seminiferous tubules of the testes also displayed a high concentration of radioactive zinc (Fig 1) The degree of radioactive uptake seemed to be closely related to the amount of contents in the ducts Where microscopic investigation revealed large amounts of ductal contents the blackening was comparatively greater than where the amounts were small The contents of the ducts in view of their relatively low tissue density, had a high uptake of radioactive zinc The contents are formed by products from the testes



Fig 2 Autoradiograph from the epididymis of a 72 year old man after incubation with $^{65}$Zn Blackened areas indicate high concentrations of radioactivity × 30

A peripheral zone of faint blackening encircling the ductal contents was seen in both the testes and the epididymes This was probably an artefact due to a shrinkage effect of the tissues during the histologic fixation The interstitial tissues of the epididymes as well as those in the testes displayed a relatively low degree of blackening A high concentration of radioactive zinc occurred in the small blood vessels in both organs

## Discussion

Autoradiographs of the testes and the epididymes in man using radioactive zinc $^{65}$Zn do not appear to have been presented earlier

The uniform and characteristic distribution of the radioactive zinc in the different sections studied was noteworthy and appeared to offer a possibility of studying the distribution of zinc in the different tissue elements of the testes and epididymes The various parts of the organs are believed to take up $^{65}$Zn in amounts corresponding to those of the natural occurring zinc during the two hours incubation in the radioactive zinc solution Metabolic events such as the transport of zinc through the epididymal ducts by products from the testes will naturally not be illustrated by this method, and experiments such as those carried out in rats by Wetterdal (1958) and by Millar, Vincent & Mawson (1961) would appear to be necessary for studies in vivo Similar experiments in man are at present unsuitable for reasons already mentioned

Unfortunately we had to study organs from elderly subjects since the removal of clinically normal scrotal contents is only exceptionally carried out in others The microscopic investigations revealed satisfactory spermiogenesis with epididymal ducts packed with spermatozoa and otherwise normal appearances The testes and the epididymes of these elderly men were thus considered suitable for use in the studies intended

The autoradiographs disclosed some interesting facts. A relatively high amount of radioactive zinc was evident in the germinal cells and in the contents of the seminiferous tubules of the testes. Earlier observations in rats by WETTERDAL (1958) and MILLAR, VINCENT & MAWSON (1961) indicated that radioactive zinc is incorporated slowly into the testicular spermatozoa. The present autoradiographs revealed high concentrations of radioactive zinc in the contents of the seminiferous tubules. It may be that the spermatozoa in man during their development in the seminiferous tubules gradually increase their supplies of zinc. The high concentration of radioactive zinc in the germinal cells indicate that these cells are the source of the zinc that will be delivered to the spermatozoa. part of the zinc accumulated in the tubules is probably attached to the seminal plasma.

The epithelium cells lining the ducts in both the caput and the cauda epididymidis showed a similar and relatively high concentration of radioactive zinc. Metabolic events such as the gradual progress of radioactive contents through the epididymal ducts will not be reproduced by the present in vitro method.

The high concentration of radioactive zinc in the epithelium cells compared to the relatively weak concentration in corresponding cells in rats 13 days after an intraperitoneal injection of $^{65}$Zn (MILLAR, VINCENT & MAWSON 1961) was an observation considered to be of importance. BIRNBAUM, HALL & LEE (1961) studied the zinc content of the sperm cells of the testes, epididymes and vas in rats and their results suggested an increasing zinc content by the processing of the spermatozoa. It may perhaps be presumed that the spermatozoa during their development in the sperm transport system receive further zinc in the epididymal ducts.

The zinc is also attached to the seminal plasma. EKBOM & WETTERDAL (1961) using paper electrophoresis studied the distribution of $^{65}$Zn added *in vitro* to human semen. The isotope was found to migrate together with a protein component supposed to be a beta globulin appearing in both fertile and infertile ejaculates. This protein bound zinc could not be shown to be significantly influenced by the number or the morphology of the spermatozoa.

**Acknowledgement**

The investigation was supported by a grant from Stiftelsen Thérese och Johan Anderssons Minne.

## SUMMARY

The testes and the epididymes of three human subjects were incubated with $^{65}$Zn in vitro. The distribution of the isotope within the different tissues was studied by an autoradiographic technique.

## ZUSAMMENFASSUNG

*Die Testes und die Epididymes von drei Fällen wurden mit* $^{65}$*Zn in vitro inkubiert Die* Verteilung des Isotopes in den verschiedenen Organen wurde *mit* Hilfe einer autoradiographischen Technik studiert

## RÉSUMÉ

Les auteurs ont incubé les testicules et les épididymes de trois sujets humains avec du $^{65}$Zn in vitro Ils ont étudié la distribution de cet isotope dans les différents tissues par une technique autoradiographique

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# AUTOMATIC ISODOSE RECORDER

by

INGEMAR LARSSON, KURT LIDEN and NILS STARFELT

In modern radiotherapeutic planning a detailed and accurate knowledge of the radiation field to be used is very important. In practice a determination of sets of isodose curves in one or several planes will give the necessary basic information and for such purposes automatic isodose plotters are invaluable. Such devices have been described by KEMP (1946), HINE, BERMAN and ELKIND (1950), MAUCHEL and JOHNS (1954), SIMONS (1956). KEMP compared the step by step integrated dosage rates of two ionization chambers, the exploring chamber moving in a cartesian system. HINE et coll. (1950) described a device with a scintillation crystal by means of which the "isocount" curves around a $\gamma$ emitting source rotating on a turntable could be recorded. The plotters described by MAUCHEL and JOHNS and by SIMONS compared two dosage rates from ion chambers. The former authors placed the moving chamber in a vertical polar system and the latter author used a vertical cartesian system.

The plotter developed by the present writers compares the dosage rates from two organic scintillators, the exploring scintillator moving in a horizontal polar system. The machine has now been successfully operated over a period of five years (LIDEN 1957). Investigations of the isodose curves of roentgen

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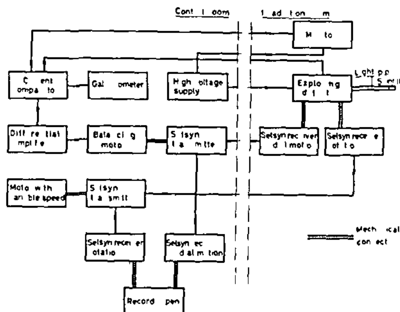


Fig 1 Block diagram of the isodose recorder

and cobalt beams, as well as of radium and tantalum applicators, have been performed

*Design of the isodose recorder* As an exploring detector the present isodose recorder utilizes a scintillator which is restricted to move in a system of polar coordinates The principle of operation is shown in Fig 1 Photographs of the actual apparatus are reproduced in Fig 2 The isodose recorder consists of two separate horizontal arms which are given a synchronous rotational motion around a vertical axis by means of a reversible motor and a Selsyn system These arms are supplied with radially movable carriages both of which are connected to the balancing motor through a Selsyn system One of these carriages carries the exploring dose detector and the other one a pen which continuously reproduces the motion of the exploring detector on a sheet of paper The mechanical mounting of the arms made of stainless steel tubes and the location of the carriages for detector and pen, are displayed in Fig 2 The origin of each polar coordinate system is adjustable The reason for this will be explained later The carriages can be moved about 50 cm in the radial direction by means of a steel wire and gear arrangement

Light from the irradiated scintillator is transmitted through a light pipe to a RCA 1P 21 photomultiplier The anode current from this photomultiplier is compared in a comparator circuit with the current from another photomultiplier receiving the light from a scintillator which is also irradiated by the source under investigation This monitor is mounted in a fixed position care

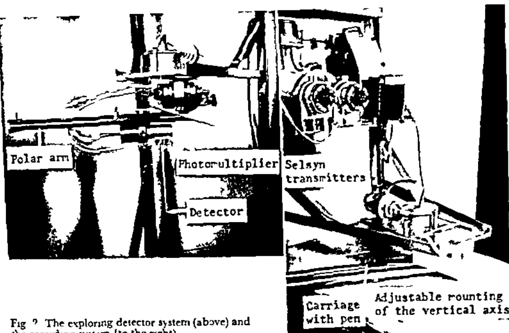



Fig 2 The exploring detector system (above) and the recording system (to the right)

being taken to ensure that the exploring detector never interferes with the radiation impinging on the monitor The variations in output from certain radiation sources necessitates the use of a monitor instead of a constant current source The monitor detector follows the variations in output and so does the exploring detector current Therefore small variations in output will not influence the curve being recorded

When the rotational motion tends to carry the exploring detector along a path which is not an isodose curve, the balance in the comparator circuit is disturbed an error signal is given to a differential amplifier and the balancing motor controlling the radial motion drives the exploring detector back to the isodose curve Thus the balance is restored and the exploring detector is forced to stay on the predetermined isodose curve This curve is recorded on a sheet of paper by the pen on the other carriage By using sufficiently long cables the exploring detector system can be mounted in the irradiation room and the recording and driving components in a shielded room

The current comparator circuit is shown in Fig 3 The galvanometer with an internal resistance of 5 kΩ can be used to measure the current in each of the two branches It has a sensitivity of 5 $10^{-10}$ A per division The dark current through the resistors $R_2 + R_3$ is balanced out by applying a certain voltage from battery B

The circuit is in equilibrium when the position of the exploring detector

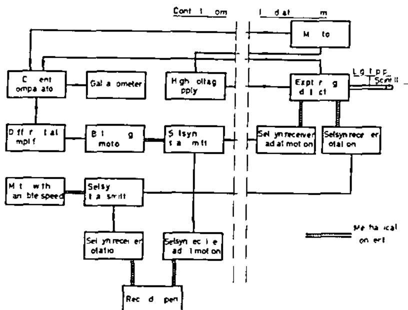


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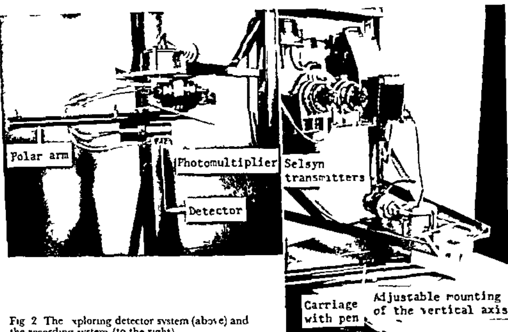



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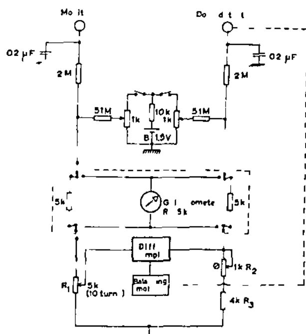



Fig 3 Current comparator circuit

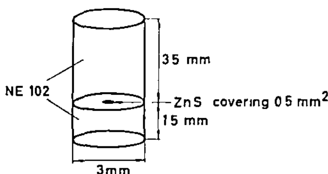



Fig 4 Compound scintillator

in the radiation field is such that the currents through the resistors $R_1$ and $R_2 + R_3$ keep the two inputs of the differential amplifier at the same voltage

The exploring detector should be able to measure small doses in roentgen units and should be small in size in order to permit a detailed study of the radiation field close to the source The detector should moreover be made of a material having a density and atomic number close to that of tissue or water in order not to disturb the radiation field under investigation In order to ensure a satisfactory operation of the differential amplifier it is important that the detector currents be sufficiently strong

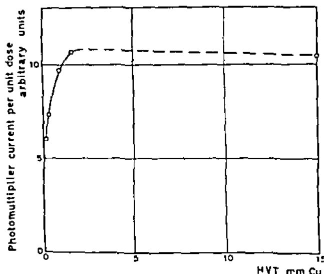



Fig 5 The dependence of the dose response on radiation quality for an anthracene crystal (diam 3 mm length 3 mm)

The light from the scintillator can most efficiently be transmitted to the photomultiplier by means of a light guide of quartz or lucite However, in this case a disturbing background may arise from Cerenkov light generated by Compton electrons in the light guide This has also been pointed out by BELCHER (1953), SHALEK and COLE (1958) In an early design two identical light guides and photomultipliers were mounted side by side but only one was supplied with a scintillator The difference between the currents from the two photomultipliers then represented the light from the scintillator itself However this arrangement requires that the photomultipliers be exactly adjusted to give the same sensitivity and that the light guiding rods be equal in performance It was found that internally polished dural tubes are quite efficient light pipes and such tubes were then used

A cylindric scintillator with a diameter of a few millimeters mounted at the end of a light pipe 20 to 50 cm in length in conjunction with a photomultiplier having a high sensitivity and low dark current fulfills all of the above requirements

Measurement in r units implies that the scintillator should always emit the same amount of light at a *certain* dose rate irrespective of the spectral composition of the radiation Therefore a review of the roentgen ray and $\gamma$ ray spectra of interest should be made In the case of a $Co^{60}$ source the radiation close to the source consists of primary $\gamma$ rays 1 17 and 1 33 MeV With increasing depth in water the relative amount of degraded radiation increases For roentgen ray spectra from roentgen generators the situation is similar but here the degraded photons dominate at much smaller depths

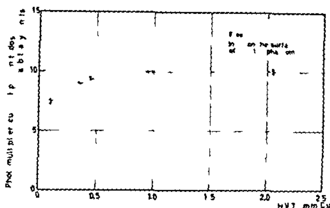


Fig 6 The dependence of the dose response on radiation quality for the compound scintillator of fig 4

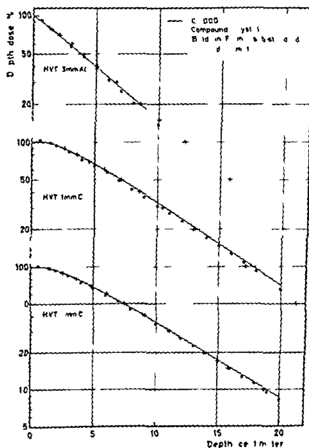


Fig 7 Comparison between measured depth dose data (+ and ) and values obtained from Central Axis Depth Dose Data (1953) (solid line)

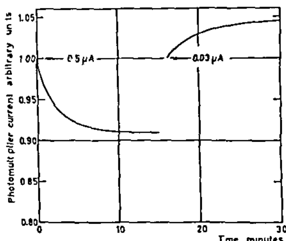



Fig 8 Photomultiplier fatigue effect At zero time the detector is placed in a radiation field giving rise to a photomultiplier current of 0 50 μA The detector is irradiated with constant intensity for 15 min and then moved to a point where the radiation field gives rise to a photomultiplier current of 0 030 μA

For $Co^{60}$ anthracene crystals can be used For radiation of lower energy special compound crystals are needed (RAMM 1956) Combinations of a plastic scintillator and $CaWO_4$ NaI or ZnS have been investigated The best results have been obtained with a scintillator, 3 mm in diameter, consisting of two pieces of solid Ne 102 plastic scintillator (Nuclear Enterprises Ltd, Edinburgh) sandwiching a very small amount of ZnS powder (Fig 4) which were heated up in an oven and pressed together The light output from this scintillator was 67 % of that obtained from an anthracene crystal 3 × 3 mm at a roentgen radiation quality of 2 mm Cu HVT The different scintillators were tested in two ways The first method involved a comparison with a simultaneously irradiated standard ion chamber both in air and on the surface of a water phantom with roentgen rays of different qualities and with a radium source (Figs 5 and 6) The relative depth dose in a water phantom for a series of primary radiations was also compared with depth doses measured by means of a Baldwin Farmer substandard roentgen ray dosemeter and with data from depth dose tables (Fig 7) The first method shows that the compound scintillator is superior to the anthracene scintillator at low energies From the second test (Fig 7) it is obvious that this scintillator can be used down to fairly great depths even with primary roentgen rays of low energy

*The photomultiplier* gives rise to the following difficulties

1 In many cases the direct radiation from the source that strikes the photo cathode and the dynodes results in a current which is not small compared to

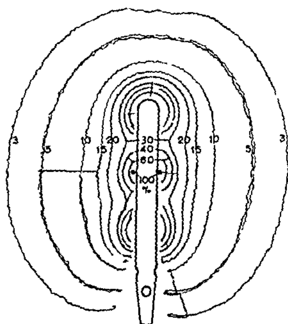


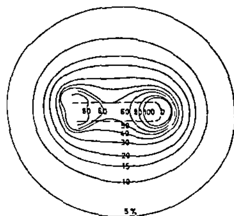

Fig 9 The system of isodose curves around a 150 mC radium applicator in a water phantom The 100 point is located 1 mm from the surface of the applicator Anthracene crystals of 1 5 and 3 5 mm diameter were used The 5 curve is recorded with both crystals

the current caused by the light from the scintillator Because the detector has to be easily movable to give a fast response to a small change in dose rate it is often difficult to shield the photomultiplier sufficiently with lead Therefore the light pipe is made as long as is convenient and a remotely controlled shutter is placed in the light pipe close to the photomultiplier so that the current from the direct irradiation of the photomultiplier can be measured at any time and compensated for electrically in the same way as for the dark current

2 To make it possible to measure low intensity radiation with small crystals and long light pipes the dark current from the photomultiplier has to be extremely low and constant Selected 1P 21 tubes have been used but at high relative air humidity the dark current has often been excessive A cut in the tube socket to increase the distance along the surface of the insulating material between the anode and the cathode was found to be helpful But nevertheless it is necessary to compensate for the dark current

3 The third difficulty is due to the fatigue effect of the photomultiplier, as demonstrated by Fig 8 It can be seen that the current approaches its steady value asymptotically It is therefore in most cases sufficient to wait two or three minutes after placing the detector in the appropriate radiation intensity before running through an isodose curve

*Operation* The recording of an isodose diagram is performed in the following way The exploring detector is placed at a point to which a certain percentage dose is ascribed from earlier measurement or by definition, for example 100 % at the surface of a phantom A high voltage is used giving a current of about



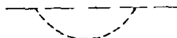



Fig 10 Isodose curves around a tantalum wire shaped as a bent hair pin The tantalum wire is shown as a line of dashes The dots and dash line in the right hand part of the figure is the plane of observation The 100 curve corresponds to 3 1 r/hr per mC

2 $10^{-7}$ A from the exploring detector For this current the fatigue effect is low and when recording at lower dose rates a change in the abovementioned current of about one per cent will give rise to a signal that is strong enough to operate the differential amplifier, thus affecting the balancing motor The dark current from the two photomultipliers is then measured with the radiation source removed and compensated for by means of the battery (see Fig 3) The battery is also used to eliminate the background current from the exploring detector caused by the source as measured with the shutter closed in the light pipe With the potentiometer $R_1$ adjusted to read the abovementioned dose rate the monitor detector is moved or its high voltage is changed until the comparator is balanced, i e until there is no output from the differential amplifier These operations are performed before the motors are connected to the transmitters of the Selsyn system After connecting the motors the exploring detector proceeds along the desired isodose curve $R_1$ is then adjusted to a new value The detector is left on the new isodose curve 2 to 3 minutes with the motors disconnected to allow for the fatigue effect in the photomultiplier If necessary the comparator is then rebalanced and a new isodose curve is recorded

It is often convenient to use two or more scintillators of different sizes when recording a set of isodose curves Close to the radiation source, where the dose rate is high, the best possible geometric resolution is desired and thus a small crystal should be used Far away from the source the isodose curves are usually well separated from one another and the accuracy can then be improved by increasing the signal through the use of a larger scintillator It may also be necessary to increase the high voltage when recording at low dose rates in order to get a sufficiently large signal As mentioned above it is the radial motion of the detector system that is influenced by the dose rate in such a way that

the detector stays on an isodose curve when the rotational motion proceeds at constant speed It is then convenient to locate the center of rotation in such a position that the dose rate decreases with increasing distance from this center for all points of the isodose curve to be recorded Otherwise the polarity of the signal to the differential amplifier has to be reversed at certain points on the isodose curve In certain cases it may be necessary to record a system of isodose curves in two or more separate runs, moving the detector coordinate system to a new position in between consecutive runs (cf Fig 10) It is for this reason that the two coordinate systems are made adjustable (Fig 2)

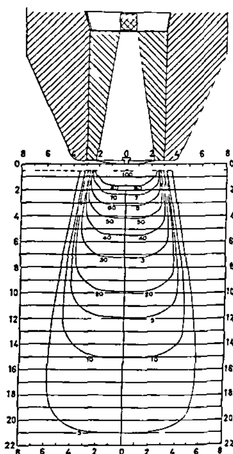



Fig 11 The system of isodose curves for a 20 curie Co unit in a water phantom FSD 10 cm field size 4 5 cm by 3 0 cm The central axis is in the plane of the diagram the 4 5 cm side of the field is parallel to this plane The 100 point is located at a point 0 5 cm below the surface of the phantom Anthracene crystals having diameters of 3 5 and 5 5 mm were used

## Discussion

The performance and accuracy of the isodose recorder can best be illustrated by discussing the systems of isodose curves obtained with some specific radiation sources Fig 9 shows a clean copy of the system of isodose curves obtained with a 150 mC Ra applicator in a water phantom The 100 % point was registered with a scintillator 1 5 mm in diameter in a 2 mm diameter container Thus this point is located only 1 mm from the surface of the applicator The 5 % curve was recorded twice using two different scintillators, the one just mentioned and a larger one with a diameter of 3 5 mm All curves corresponding to a dose rate higher than 5 % were run with the small detector and the 3 % curve with the large one

Bladder tumours are sometimes treated with the radiation from implanted radioactive tantalum wires, $Ta^{182}$ A wire in the form of a somewhat bent hair pin is implanted in the wall of the bladder by means of a special instrument The dose delivered in this treatment was earlier determined only by theoretical calculation The accuracy of treatment planning has been considerably

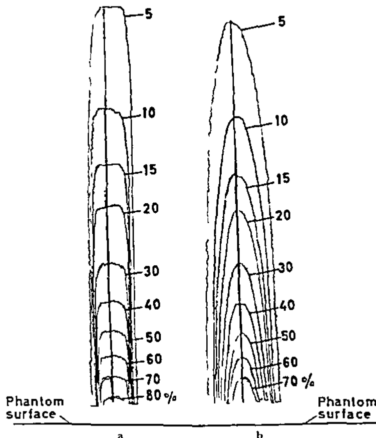



Fig 12 Isodose curves with narrow beams of roentgen rays with 40 cm FSD and 1 mm Cu HVT with a 1 cm diaphragm on the surface of the phantom (a) and with the diaphragm located 27 cm from the focus (b) giving a geometric field of 1 cm on the phantom surface The position of the 70 point on the central axis was determined from zero-field data tabulated in Central Axis Depth Dose Data (1953) A compound scintillator was used (dimensions diam 3 mm length 4 mm)

improved by using recorded systems of isodose curves in different planes around both straight and bent tantalum needles in a water phantom (Fig 10) Absolute determination of the dose rate has been made by means of micro-ionization chambers (SIEVERT 1934 SKOLDBORN 1959) calibrated with a standard radium source The 20 curie $Co^{60}$ unit in Lund which was used for treatment at a *FSD up to 10 cm was equipped with collimators for rectangular fields* The radiation field obtained with these collimators was studied with the isodose recorder Systems of isodose curves were recorded in different planes As an example of the results of these measurements the isodose curves in a plane through the axis of the collimator and parallel to the longest side of

the rectangular field is shown in Fig 11 The 100 % point was located at a depth of 0 5 cm below the surface of the phantom

The last example is chosen in order to illustrate the effect on the dose distribution of the position of the diaphragm when using a narrow beam from a roentgen tube having a 1 2 cm focus (Fig 12)

Finally it should be mentioned that for all the cases now discussed dose rate (e g r/hr or r/min) can be ascribed to the isodose curves registered This may be done either by absolute calibration of the detector or by determining the dose rate by means of an ionization chamber at one point on an arbitrarily chosen isodose curve

## Acknowledgements

The authors are greatly indebted to Dr J Cederlund for valuable assistance The investigation was supported by grants from the Swedish Cancer Society

## SUMMARY

The design and operation of an automatic isodose recorder is described The recorder compares the electric currents produced by the simultaneously irradiated monitor and exploring probe the latter being restricted to move in a system of polar coordinates The probe consists of a small exchangeable organic or compound scintillator 1 to 6 mm in diameter *connected to a RCA 1P 21 photomultiplier through a light transmitting tube* Systems of recorded isodose curves for radium and Ta 182 applicators and for roentgen and $Co^{60}$ beams are shown indicating good reliability and flexibility of the equipment

## ZUSAMMENFASSUNG

Die Konstruktionen und die Funktion eines automatischen Isodosenschreibers werden beschrieben Der Schreiber vergleicht die elektrischen Strome die in einem stationaren Monitor und in einem beweglichen Detektor produziert werden die Bewegung des letzteren geschieht in einem polaren Kordinatensystem Der bewegliche Detektor besteht aus einem kleinen auswechselbaren organischen oder kombinierten Szintillator 1 bis 6 mm in Diameter *der durch einen Lichtleiter an einen RCA 1P 21 Sekundarelektronenvervielfacher angeschlossen* ist Die jenige Systeme von Isodosenkurven die fur Radium und Ta 182 Applikatoren und fur Rontgen und $Co^{60}$ Strahlung registriert sind zeigen dass die Apparatur zuverlassig und vielfach verwendbar ist

## RÉSUMÉ

Les auteurs décrivent la construction et le fonctionnement d un inscripteur automatique de courbes isodoses L inscripteur compare les courants électriques produits par le monitor et une sonde exploratrice irradiés simultanément la sonde étant astreinte à se déplacer dans un système de coordonnées polaires La sonde est faite d un petit scintillateur organique ou composé interchangeable d un à six millimètres de diamètre relié à un photomultiplicateur RCA 1P 21 par un tube transmetteur de lumière Les auteurs présentent des systèmes de courbes isodoses enregistrées avec cet appareil pour des applicateurs de radium et de Ta 182 et pour des rayonnements roentgen et du $Co^{60}$ ces courbes montrent la fidélité et la maniabilité de cet appareil

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# ROLE OF TRAUMA IN THE DEVELOPMENT OF MALIGNANT BONE TUMOURS

by

CARL KREBS and KAJ OLSEN

It has been established that exposure to radiation and to chemical, thermic and hormonal stimuli may have a cancerogenic effect (2, 3) and that chronic infection may occasionally be complicated by neoplastic changes (12) Under experimental conditions the latent period for the development of transplantable tumours is apparently shortened when the animals are exposed to repeated surgical trauma (5) although tumours have scarcely ever been induced without the contributory action of co carcinogens (8, 10) A few authors state however, that this may occur in rare cases (11)

The cancerogenic importance of traumatic injury in the development of malignant tumours mentioned in the older textbooks (1, 14) presumably arose from the patients statements that a definite injury provoked the malignant condition

The numerous major and minor injuries of everyday life may readily be forgotten but a certain incident will more easily be remembered if a pathologic change that was not noticed although perhaps present at the time of the injury became evident shortly afterwards There are certain other factors that are relevant A tumour bearing limb will often unnoticed by the patient, be slightly asynergic and thus be more liable to injury The limb is often hypersensitive, so that even slight injury may produce relatively severe pain or tenderness It

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might also be mentioned that modern insurance conditions may influence the patient's attitude since his financial position will be more favourable after an accident than he would be with other conditions Long term observations (5, 6) of patients who during World War I were exposed to severe trauma showed an incidence of malignancy in the order of one in 700 i e analysis of this large series revealed no obvious increase in morbidity as compared with corresponding groups of the general population

Poulsen (13), in a review of the files of the Directorate of Accident Insurance in Denmark for the years 1931—1940, found 86 cases with the diagnosis of cancer, including 29 accepted as caused or aggravated by traumatic injury The records of the Radium Centre of Copenhagen for the same period recorded a history of trauma in 14 of 40 cases of bone tumours A critical re appraisal of these two series shows however, that in only one case of each series is it impossible to rule out that the disease had been caused by the injury The tumours occurred in the age groups in which the highest cancer incidence is generally found

An analysis of 168 cases of malignant bone tumours was as follows

| Clinical no e | 1935—1949 | 1950—1959 |
|---|---|---|
| Trauma sustained | 28 | 33 |
| Pathologic fracture | 8 | 6 |
| No trauma | 52 | 43 |
| No information as to trauma | 6 | 6 |

The results of re appraisals of previous roentgenograms in four cases are reported below The subjects were assumed to be in good health at the time when the trauma was sustained The pathologic changes present were missed at the first roentgen examination the presence of a tumour not being revealed until after the lapse of several months If the original films had not been available the case history would have indicated that the new growth was caused by the injury In addition a fifth case illustrates how metastases may select a site where traumatic injury has been sustained

*Case 1* Man aged 21 who sprained his right ankle during military service (Fig 1a) The ankle was put in plaster and three control roentgen examinations were performed

Four months after the injury an osteogenic sarcoma became apparent at the site and metastases were found in the lungs The patient was eventually admitted to the Radium Centre (Fig 1b) Death occurred 3 years later

*Case 2* Boy aged 13 who sustained a fracture of the left humerus in a fall (Fig 2a) Uncomplicated union with complete restoration of function occurred after immobilisation Four months later a swelling of the shoulder was noticed and an osteogenic sarcoma was diagnosed (Fig 2b) Death ensued 17 months after the injury

*Case 3* Boy aged 16 sustained a transverse fracture of the femur while playing football (Fig 3a) He was treated with extension and three and a half months later could walk with



Fig 1 Case 1 *Left* A.p and lateral views following trauma Superficial destruction with spicule formation at the posterior aspect of the distal part of the tibia *Right* 7 months later Tumour with separation of the syndesmosis

the support of a stick. A further fracture occurred at the same site six months after the trauma and a bone tumour was then detected Biopsy was not performed The patient is still alive (Fig 3b)

*Case 4* Boy aged 3 years was examined because of a minor trauma to the right shoulder no evidence of fracture Four months later swelling of the right upper arm occurred and a Ewing sarcoma involving the entire diaphysis was apparent Death ensued 14 months after the accident. Re appraisal of the first films showed fine periosteal thickening 10 cm in length of the shaft of the humerus i e signs of the incipient tumour

*Case 5* Man aged 35 noticed a swelling of the right eighth rib and thought that it had been caused by an injury sustained two years previously Clinical examination revealed a Ewing sarcoma of the rib which subsided after roentgen therapy and the rib was resected three months after the commencement of the treatment




Fig 2 a) Spiral fracture of the humerus with an area of destruction in the neck due to an osteogenic sarcoma b) Four months later

The patient later stated that he had had a lump on his scalp for some months Roentgen examination of the skull revealed bone destruction at the site of the tumour all the changes rapidly disappeared following roentgen irradiation The patient died with extensive metastases 33 months after the first admission It is probable that the lesion of the rib was actually a metastasis situated in a locus minoris resistentiae that had occurred after the trauma and that the primary growth was in the calvarium

## Discussion

A deep seated (or merely subcutaneous) tumour is not likely to be palpable until it consists of at least $10^9$ tumour cells (weighing less than 1 g) The minimum time of generation for cell division is about 20 hour under experimental conditions in tissue culture and there is nothing to suggest that the growth rate is higher in vivo On the assumption that the time of generation is 24 hours and that no cells die but all contribute to the expansion of the tumour $10^9$



Fig 3 a) Malignant destruction around the site of fracture b) and c) Six months later The changes have advanced

cells will have developed after 10 days $10^{6}$ in three weeks and $10^{9}$ within a month

Assuming that a normal cell may become malignant after exposure to trauma a tumour induced in this way can arise from only one or a few cells The growth rate of bone tumours at the time of diagnosis is fairly well known — a tumour does not double in size from day to day It is therefore improbable that extremely rapid growth occurs in the earliest stages of the development of a tumour Several cells may of course simultaneously participate in the development of a tumour but some months will presumably be required before it attains a palpable size Accordingly if a bone tumour is diagnosed earlier there is every probability that it existed at the time when the trauma was sustained

An incipient tumour as already mentioned may very well consist of $10^{7}$ cells or more without being detectable If such a tumour is exposed to mechanical trauma its capsule may rupture and massive spread occur due to (1) liberation of malignant cells by the injury (2) vascularisation before and during the re absorption of a haematoma i e more portals for metastases are created, (3) the pressure within the tissue and hence the tendency to metastases being increased by extravasation

Reparative processes with or without inflammation constitute a stress on the normal resistance of an organism and surgical procedures may possibly have a similar effect

It is known that tumour cells are constantly circulating in the blood stream in cases of malignancy The host organism is, to an appreciable extent, capable of destroying such cells, so that the development of metastases occurs only in exceptional cases during the early stages of the disease (9) After exposure to trauma, much of the physiologic reserve may be expended in reparative processes and favourable conditions for the development of secondaries created at the site of the contusion (10), and in this fertile soil a secondary tumour may develop (Case 5)

Theoretical considerations would thus appear to be against the assumption of a causal relationship between trauma and the development of neoplasms Injury may aggravate an existing neoplasm, but this may be an advantage in that the patient may seek aid earlier than he would otherwise have done (traumatic determinism)

The case histories reported confirm Ewing s words ' Trauma reveals more malignant growth than it produces (4)

## SUMMARY

The possible significance of trauma in producing or aggravating malignant bone tumours is discussed

## ZUSAMMENFASSUNG

Der mogliche Einfluss von Trauma auf die Entstehung und Verschlimmerung von malignen Geschwulsten wird diskutiert

## RÉSUMÉ

Les auteurs étudient l influence possible des traumatismes sur l apparition ou l aggravation des tumeurs osseuses malignes

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# LEUCOCYTE MIGRATION IN PARTIAL BODY IRRADIATION OF GUINEA PIGS

by

B TRIBUKAIT A FORSSBERG and CHRISTINA ÖSTERDAHL

White cells are extremely motile and may readily be caused to migrate from the blood circulation to depot tissues such as the bone marrow or capillary beds (Cf Ciba Foundation Symposium on Haemopoiesis London 1960 and DOUGHERTY 1952) Whole body irradiation of animals causes within the first few hours an increase of leucocytes except of lymphocytes in the circulation (HULSE 1960) a reaction which is due to a release of cells from depot tissues This is a transient stage and within a few hours it is followed by a general decrease, the well known effect in radiation work The initial rapid concentration changes are in themselves of interest, however as an indication of early changes produced by irradiation

The complexity of these phenomena was discussed in a previous publication (FORSSBERG, TRIBUKAIT & VIKTERLOF 1961) An increase in some leucocyte groups and a fall in others were observed reactions that were clearly dose dependent Species differences between guinea pigs and mice were also noted

It is demonstrated in the present investigation that partial body irradiation even of relatively small areas may initiate specific reactions of segmented cells and lymphocytes that have been forced into the blood circulation The studies were confined to guinea pigs as these animals are best suited to such procedures and are also more radiation sensitive

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*Material and Methods* The guinea pigs were of the same origin as previously used, the average weight of the animals at the time of the irradiation was in all series, excepting one, about 175 to 225 g In one series 400 g animals were used but this weight increase caused no difference in the reactions The irradiations were given under the same running conditions as previously 250 kV, 15 mA, HVL 1 6 mm Cu, dose rate 110 rad/min, as measured on the surface of the irradiation fields The whole body irradiations were in our previous studies given in three sets, over the left and right flanks and over the dorsal side As this was not possible in the partial body program, all irradiations even the whole body doses were given in one delivery The rest of the animal was lead shielded in the partial body irradiations Comparison was made between irradiations of small abdominal fields as specified on p 52, and whole body irradiations In both procedures the beam was directed towards the abdomen and the doses were given under ether anaesthesia Simultaneously, control groups of normal but sham treated, as well as anaesthetized and sham treated animals, were run We had to confine our observations to the effects at one dose level, 300 rad and at a single time of four hours after irradiation at which time it had previously been found, the effects are well expressed

*The evaluation of the results was based entirely on the two large groups of* segmented cells and lymphocyte cells although differential counts on all the white cell groups were made The rods and monocytes mainly followed the segmented cells in their reaction pattern but in this limited material the numbers were too small for statistical treatment The previous work should be consulted for other experimental details

## Results

Several sets of experiments from a general survey to a more detailed analysis in a particular case, were performed

The control group (1) and the whole body irradiation group (2) were in the first series compared with groups of animals which had received irradiation as follows (3) the head including the upper part of the shoulders (4) a middle part including the lungs and abdomen and (5) the hind quarters up to and including the hips A further group (6) in which the intestines and the greater part of the lungs were lead shielded while the head and hind quarters received irradiation, was also compared This latter group was selected to be approximately equal to the middle part (group 4) in regard to body volume All doses were given from the dorsal side Anaesthesia was not necessary in these experiments since the animals remained quiet in the irradiation cages The data are presented in Table 1 (series I)

An increase of segmented cells occurred in all the groups but there is no clear relationship between the percentage of the irradiated body volume and that of the released cells Although the head and hind part are each by volume

**Table 1**

*Series I Whole body and partial body irradiation of groups of guinea pigs 10 animals in each group The number of segmented cells and lymphocytes per mm³ in the blood 4 hours after 300 r irradiation and the percentage concentration is given*
*Series II Left side and right side irradiation similar data as in series I Two sets of experiments with 10 animals in each group*

| Series | Group | Approximate irrad | Segmented | | Lymphocytes | |
|---|---|---|---|---|---|---|
| | | | n | | n | % |
| | (1) controls | — | 654 ± 138 | 16 4 | 3 167 ± 347 | 81 5 |
| | irrad of | | | | | |
| | (2) whole body | 100 | 2 430 ± 495 | 42 5 | 2 414 ± 516 | 45 7 |
| I | (3) head | 70 | 1 663 ± 367 | 31 1 | 3 107 ± 403 | 63 7 |
| | (4) middle part | 60 | 2 977 ± 580 | 47 3 | 2 506 ± 395 | 41 7 |
| | (5) hind | 20 | 1 661 ± 283 | 32 3 | 3 195 ± 416 | 61 9 |
| | (6) head+hind | 65 | 2 748 ± 457 | 34 6 | 4 559 ± 800 | 58 4 |
| | (1) left side | 50 | 1 973 ± 479 | 25 1 | 5 533 ± 930 | 70 8 |
| II | (2) » » | | 1 922 ± 393 | 24 7 | 5 424 ± 470 | 70 6 |
| | (1) right side | 50 | 4 669 ± 895 | 41 3 | 5 971 ± 1 006 | 53 4 |
| | (2) » » | | 2 966 ± 341 | 39 7 | 4 077 ± 416 | 53 9 |

weight not more than about 20 % of the total weight of the whole body, the figures for segmented cells are substantially higher than might be expected on a simple proportional basis The reactions of these two different parts are, however very similar in regard to segmented cells Irradiation of the middle part of the body and the combined head and hind part on the other hand, making up some 60 to 65 % of the body is followed by an increase of segmented cells which is at least as high as after whole body irradiation The behaviour of the lymphocytes is not so well expressed because of the somewhat small effects from the irradiation It should be noted, however that only an irradiation of the middle part seems to cause the fall usually found after whole body doses and that in the group head and hind (group 6) the concentration of lymphocytes is high and suggests a possible release of these cells

In two sets of experiments two groups of animals each of 10 guinea pigs were irradiated over a left and a right side dorsal field with the other longitudinal half of the body lead shielded (Table 1 series II) The control group and the whole body irradiated group were omitted in this series The figures for segmented cells and lymphocytes in the first right field irradiation (4 669 5 971 in Table 1) are probably exaggerated since two animals had an extraordinarily high leucocyte level It may be noted that calculated on a percentage basis the two sets of experiments produced similar results irrespective of the variations in the absolute values

**Table 2**

*Significance of the migration of segmented cells and lymphocytes into the circulation when the two abdominal fields were irradiated as compared to each other whole body irradiation or controls*

| Cells | Irrad. field | Compared with | Mean change | Animals n | Significance P |
|---|---|---|---|---|---|
| Segm. | Right | Left | + 184.9 | 48 | < 0.001 |
| » | » | Whole body | — 11.3 | 37 | ~ 0.[illegible] |
| Lymph. | Left | Right | + 19.9 | 48 | 0.01 |
| » | » | Control | + 48.3 | 37 | 0.005 |
| » | Right | » | + 3.3 | 37 | 0.2–0.3 |

The data suggest that segmented cells are released in greater amounts following right side irradiation. The difference, even in this limited material, is significant on the P = 0.01 level. The lymphocyte concentration is generally high. In view of the fact that the normal concentration is in the order of 3 000 cells and that whole body irradiation causes a further decrease, it appears likely that irradiation of only a longitudinal half of the body produces a release of those cells.

By far the greater part of the liver is involved when the right side of the body is irradiated, whereas only minor parts are affected by left side irradiation. On the other hand, left side irradiation means a substantial irradiation of the intestines and the spleen. The possible role of the spleen was taken into consideration in a group of animals irradiated 6 days after splenectomy had been performed. Splenectomy caused a marked increase in the circulating lymphocytes (about 60 %) but no changes in the segmented cells. An average increase in the segmented cells and a fall in lymphocytes as an outcome of the irradiation is no indication that the spleen has taken part in these reactions. Since in both instances the suprarenals got equal irradiation they may also be assumed to exert no influence.

An appraisal of the experiments now described, although not conclusive, leads to the working hypothesis that a difference exists in the response of the segmented cells to right and left side irradiations. As in the initial trials no significant data were obtained by irradiation of the head and hind parts attention was directed to the middle part of the body.

A definite attempt to ascertain if in a particular case partial body irradiation might initiate specific reactions was made as follows. The irradiated body volume was further limited by using right and left fields of 2.5 cm × 3 cm. Animals under ether anaesthesia were used. The two fields, right and left, were placed over the right upper part of the abdomen (liver region) and over

the left inferior part of the abdomen (intestinal region), respectively The spleen thus received only a small percentage of stray irradiation while each of the suprarenals were in the irradiation fields

The anaesthetic in itself appeared to produce no changes in the white cells in guinea pigs and the mean values for total leucocytes, and for segmented cells and lymphocytes, did not differ by more than ± 4 % from each other in normal and ether treated animals Nevertheless anaesthesia seems to have a slightly moderating effect on the action of the irradiation, this was at least sug gested in the motile segmented group where the outflow of cells was about 25 % lower The difference is significant with a probability of P = 0 01

Statistical analyses of the series of right and left field irradiations, as com pared to whole body doses and controls were performed in all the combina tions that are relevant to the discussion (Table 2) The most marked difference in reaction occurred among the segmented cells in which a right field, as compared to a left field irradiation produced a very high additional outflow In fact although the irradiated field comprised only about 5 % of the body, the release of segmented cells was not significantly different from that following the whole body irradiation An outflow of lymphocytes was initiated by the left field irradiation and a significant increase of about 50 % over the normal level was recorded There was also evidence that more lymphocytes were forced into the blood circulation following left field irradiation as compared to right field irradiation The difference in lymphocyte concentration is more over negligible when the right field program is compared with the normal values

## Discussion

The initial reactions of the white cells following partial irradiation seems to proceed in a different way, as compared to the whole body irradiations The effect is in a sense specific since irradiation over a right field causes a strong outflow of segmented cells whereas irradiation over a similar area on the left side of the abdomen produces a flow of lymphocytes The selection of these two fields was made more or less by trial and error The specificity as regards the migration of segmented cells and lymphocytes is therefore probably not confined to the present irradiation program The phenomenon as such means a further complication in the analyses of blood reactions shortly after an irradia tion Considered from the practical point of view it should be observed that the results of early analyses of the blood values of irradiated human subjects will depend on what parts of the body have been irradiated Uniform whole body irradiation is rarely attained and analyses of human cases at an early stage is therefore likely to yield fortuitous results

The results in the segmented group are uniform in the sense that all the irradiation programs produced an increase in cells in the blood circulation

**Table 2**

*Significance of the migration of segmented cells and lymphocytes into the circulation when the two abdominal fields were irradiated as compared to each other, whole body irradiation or controls*

| Cells | Irrad. field | Compared with | Mean change | Animals n | Significance P |
|---|---|---|---|---|---|
| Segm. | Right | Left | + 184 9 | 48 | < 0 001 |
| » | » | Whole body | — 11 3 | 37 | ~ 0 2 |
| Lymph. | Left | Right | + 19 9 | 48 | 0 01 |
| » | » | Control | + 48 3 | 37 | 0 003 |
| » | Right | » | + 3 3 | 37 | 0 2—0.3 |

The data suggest that segmented cells are released in greater amounts following right side irradiation The difference even in this limited material is significant on the P = 0 01 level The lymphocyte concentration is generally high In view of the fact that the normal concentration is in the order of 3 000 cells and that whole body irradiation causes a further decrease, it appears likely that irradiation of only a longitudinal half of the body produces a release of those cells

By far the greater part of the liver is involved when the right side of the body is irradiated, whereas only minor parts are affected by left side irradiation On the other hand left side irradiation means a substantial irradiation of the intestines and the spleen The possible role of the spleen was taken into consideration in a group of animals irradiated 6 days after splenectomy had been performed Splenectomy caused a marked increase in the circulating lymphocytes (about 60 %) but no changes in the segmented cells An average increase in the segmented cells, and a fall in lymphocytes, as an outcome of the irradiation is no indication that the spleen has taken part in these reactions Since in both instances the suprarenals got equal irradiation they may also be assumed to exert no influence

An appraisal of the experiments now described, although not conclusive, leads to the working hypothesis that a difference exists in the response of the segmented cells to right and left side irradiations As in the initial trials no significant data were obtained by irradiation of the head and hind parts, attention was directed to the middle part of the body

A definite attempt to ascertain if in a particular case partial body irradiation might initiate specific reactions was made as follows The irradiated body volume was further limited by using right and left fields of 2 5 cm × 3 cm Animals under ether anaesthesia were used The two fields, right and left were placed over the right upper part of the abdomen (liver region) and over

the left inferior part of the abdomen (intestinal region), respectively The spleen thus received only a small percentage of stray irradiation while each of the suprarenals were in the irradiation fields

The anaesthetic in itself appeared to produce no changes in the white cells in guinea pigs and the mean values for total leucocytes, and for segmented cells and lymphocytes, did not differ by more than $\pm 4$ % from each other in normal and ether treated animals Nevertheless, anaesthesia seems to have a slightly moderating effect on the action of the irradiation, this was at least suggested in the motile segmented group where the outflow of cells was about 25 % lower The difference is significant with a probability of $P = 0\ 01$

Statistical analyses of the series of right and left field irradiations as compared to whole body doses and controls were performed in all the combinations that are relevant to the discussion (Table 2) The most marked difference in reaction occurred among the segmented cells in which a right field, as compared to a left field irradiation, produced a very high additional outflow In fact although the irradiated field comprised only about 5 % of the body the release of segmented cells was not significantly different from that following the whole body irradiation An outflow of lymphocytes was initiated by the left field irradiation and a significant increase of about 50 % over the normal level was recorded There was also evidence that more lymphocytes were forced into the blood circulation following left field irradiation as compared to right field irradiation The difference in lymphocyte concentration is moreover negligible when the right field program is compared with the normal values

## Discussion

The initial reactions of the white cells following partial irradiation seems to proceed in a different way, as compared to the whole body irradiations The effect is in a sense specific since irradiation over a right field causes a strong outflow of segmented cells whereas irradiation over a similar area on the left side of the abdomen produces a flow of lymphocytes The selection of these two fields was made more or less by trial and error The specificity as regards the migration of segmented cells and lymphocytes is therefore probably *not* confined to the present irradiation program The phenomenon as such means a further complication in the analyses of blood reactions shortly after an irradiation Considered from the practical point of view it should be observed that the results of early analyses of the blood values of irradiated human subjects will depend on what parts of the body have been irradiated Uniform whole body irradiation is rarely attained and analyses of human cases at an early stage is therefore likely to yield fortuitous results

The results in the segmented group are uniform in the sense that all the irradiation programs produced an increase in cells in the blood circulation

It is however noteworthy that so many procedures whole body, middle part, head and hind part, as well as small right field irradiation, all produce an outflow of segmented cells that is of about the same order of magnitude although the irradiated volume varies up to a ratio of 1 20 (see Table 1) The same holds probably true when the right half of the body is irradiated The release of segmented cells seems then to be regulated through a mechanism that in the main works independently of the body volume irradiated

The reaction of lymphocytes is in principal different An increase in lymphocytes does not appear to occur after whole body irradiation In our previous material of guinea pigs and mice, lymphocytes started to decrease from the very *earliest observations one hour after irradiation*, provided the dose reached a certain level The present material clearly indicates that lymphocytes can be stimulated to an outflow by a left field irradiation over the abdomen, and possibly also by other procedures (cf Table 1) Because of the omission of controls and a whole body irradiated group, in series II of Table 1, these lymphocyte values cannot be discussed in a conclusive way The data in Table 2 proves however, with satisfactory significance the specific reaction of the lymphocytes following a left field dose

It would appear that the outflow of cells takes place from the irradiated tissue, although the hypothesis of a stimulated release from other parts of the body cannot be eliminated There is ample evidence that irradiation may cause profound changes in the structure and permeability of tissue membranes especially those that are built up of mucopolysaccharides BRINKMAN et coll (1 2 3) have shown that carefully prepared membranes, when irradiated *in vitro* respond rapidly with an increased penetration rate for a limited period of time The mechanism seems to involve a partial depolymerization of the mucopolysaccharides Clearly here a neuro hormonal mechanism is eliminated Provided similar reactions take place in the intact body — which so far has not been demonstrated — the passage of cells through the barriers of the tissue could be facilitated since the authors noticed that occasionally large particles like red cells could pass through holes in the membranes

If the hypothesis of a direct outflow from the irradiated tissues be accepted the reaction of the lymphocytes in left field irradiation is not altogether clear One has to consider that a whole body dose of 300 r causes a decrease in lymphocytes and that then also the left field is included It may be that also after whole body irradiation an outflow of lymphocytes proceeds from the region of tissues on the left side but *that this is masked by the predominating* reaction from the major part of the body which may be supposed to favour the opposite reaction, i e a disappearance of lymphocytes from the blood circulation Another explanation may be that whole body irradiation generally prevents release of lymphocytes into the blood, a mechanism that might conceivably be controlled by hormones We have so far not performed any experiments to verify this hypothesis

There is however evidence of a hormonal control of at least the leucocyte concentration in the circulation as has also been reported by DOUGHERTY (1952, 1959) When the cortisone in the peripheral blood decreases below a certain level the lymphocytes increase in number, and vice versa A transient lymphocyte increase, rather similar to that found in the present investigation may also be produced by stress reactions e g following the administration of epinephrine It is, however not known at present whether the resemblance between the radiation induced and the hormonally controlled migrations is more than an incidental one

## Acknowledgements

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## SUMMARY

The concentration of segmented cells and lymphocytes in the blood four hours after partial body irradiation in guinea pigs was found to differ markedly from that following a whole body dose The significance of the high release of segmented cells into the blood that occurred when a small field over the right side of the abdomen was irradiated as compared to the release of lymphocytes that was observed after a similar left sided irradiation is discussed

## ZUSAMMENFASSUNG

Die Anzahl von segmentierten Blutzellen und Lymphocyten schwankt betrachtlich vier Stunden nach Bestrahlung jenachdem ob die Meerschweinchen total oder nur lokal bestrahlt wurden Die betrachtliche Ausschwemmung von segmentierten Leukocyten in den Blutstrom nach lokaler Bestrahlung des rechten Abdomens steht im Gegensatz zu der hohen Ausschwemmung von Lymphocyten nach Bestrahlung der linken Bauchhalfte

## RÉSUMÉ

Le nombre des polynucléaires et des lymphocytes dans le sang de cobayes quatre heures après irradiation partielle du corps diffère notablement de celui que l on trouve apres irradiation de tout le corps Les auteurs étudient la signification de l importante polynucléose sanguine qui survient apres irradiation d un petit champ du côté droit de l abdomen et la comparent a la lymphocytose observée après une irradiation analogue du coté gauche

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FROM THE NATIONAL BUREAU OF STANDARDS, WASHINGTON, D C, U S A LABORATOIRE DE DOSIMETRIE, PARIS FRANCE, THE PHYSIKALISCH TECHNISCHE BUNDESANSTALT BRAUNSCHWEIG, GERMANY, AND THE NATIONAL PHYSICAL LABORATORY, TEDDINGTON ENGLAND

# INTERCOMPARISON OF NATIONAL ROENTGEN AND GAMMA RAY EXPOSURE-DOSE STANDARDS

by

H O WYCKOFF A ALLISY G H ASTON G P BARNARD W HUBNER, T LOFTUS and G TAUPIN

Many national laboratories maintain free air ionization chambers for the measurement of exposure dose in roentgens In the past, accurate comparison of these chambers was not possible without the transport of one of the standards to another laboratory where a direct comparison of the instruments was made Because of the considerable cost and time involved such intercomparisons have not been frequent On the other hand intercomparisons between national laboratories are necessary to assure worldwide agreement A more readily portable instrument of sufficient calibration stability for use as a transfer instrument is therefore desirable This instrument should also be usable in the higher energy regions for example with cobalt 60 and cesium 137 gamma rays

At the 1956 meeting of the International Commission on Radiological Units and Measurements (ICRU) the U S National Bureau of Standards agreed to construct and calibrate a small cavity chamber a defining diaphragm and a charge compensating capacitor for such indirect intercomparisons A similar kit has been constructed for the United Nations

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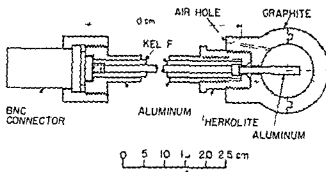



Fig 1 Cross-sectional view of cavity chamber used on these intercomparisons

Educational, Scientific, and Cultural Organization These kits are made available to the various national laboratories for intercomparison purposes

The present paper reports the results of the calibration of the ionization chamber instruments by four national laboratories (The results of the diaphragm and capacitor intercomparison are reported elsewhere) These laboratories were chosen for the first calibration because there has been a direct intercomparison between two (U K National Physical Laboratory NPL and U S National Bureau of Standards NBS) of the national standards (ASTON and ATTIX 1956) and indirect intercomparisons between two (French Laboratoire de Dosimetrie LD and U S National Bureau of Standards) of these laboratories (ALLISY et coll 1957) and the fourth laboratory (German Physikalisch Technische Bundesanstalt PTB) is in the same geographical region It was hoped that a comparison of the data obtained with the small cavity chambers with that previously reported might indicate the adequacy of the cavity chambers for such intercomparisons The calibration data are reported in some detail By the comparison of data taken at different times by the same laboratory with the same quality of radiation one may obtain some idea about the reproducibility of calibration One may also examine the data to see if there is a trend in the calibration with the geometrical arrangement which is somewhat different in the various laboratories

## Experimental arrangements

A cross sectional view of one of the cavity chambers is shown in Fig 1 It is a three terminal chamber so that the same current measuring system can be used for it as for the standard instrument The wall is about 4 mm thick so that electronic equilibrium will exist even for cobalt 60 gamma rays The diameter of the aluminum center electrode is adjusted empirically so as to reduce the energy dependence as far as possible (Subsequent work

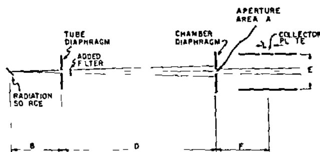



Fig 2 Schematic view of experimental arrangement at each of the national laboratories during the X ray calibrations The principal dimensions are labeled The plate height of the par all l plate free air chamber is dimension G (See Table 1 for numerical values for each of these dimensions The principal dimensions of the cylindrical standard at PTB are given in fig 3)

with the plastic mixture suggested by SHONKA et coll 1958 indicates a similar energy dependence with the plastic) The ionization collecting potential is applied between the graphite shell and the aluminum tubing Tests of saturation indicate that the lack of saturation is only about 0 1 per cent for dose rates of the order of a few roentgens per minute when 300 volts are used as the collector potential All calibrations are therefore made with a 300 volt collecting potential and saturation corrections for this chamber are neglected

Ionization currents are determined for each polarity of collecting potential The average of these two currents is reported In this way extracameral effects are eliminated and the effect of leakage from strained insulators is reduced

The schematic arrangement for the measurement of the roentgen beam with a free air chamber at each of the national laboratories is indicated in

**Table 1**

*Principal parameters for free air standard measurements at the laboratories in France Germany U K and the U S*

| Parameters* | A (cm²) | B (cm) | D (cm) | F (cm) | L (cm) | E (cm) | G** (cm) | Field strength v/cm | Field distorsion ($k_f$) |
|---|---|---|---|---|---|---|---|---|---|
| France | 0 7758 | 14 5 | 119 5 | 22 5 | 6 003 | 16 | 20 | 125 | 1 000 |
| Germany | 0 7879 | 36 | 100 2 | 48 1 | 25 122 | *** | *** | *** | 1 004 |
| U K | 0 8139 | 25 | 50 | 52 4 | 10 043 | 30 | 30 | 100 | 1 0006 |
| U S | 0 7855 | 20 | 130 | 50 8 | 10 08 | 20 | 26 8 | 240 | 1 000 |

* See Fig 2 for interpretation of the letters
** G is the collector plate height
*** See Fig 3

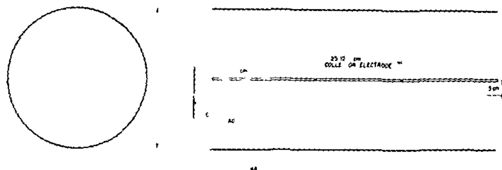


*Fig. 3. Schematic view of experimental arrangement at PTB for X ray calibration. A collecting potential of 3 kV is used and the field strength at radius r is given by*

$$\frac{3000}{r \ln \left(\frac{4.0}{0.7}\right)} \text{ V cm}^{-1}$$

Fig. 2. The important dimensions are indicated by letters. The numerical values for each of the dimensions at each national laboratory are indicated in Table 1. The important dimensions for the cylindrical standard at the PTB are indicated in Fig. 3. Two of the laboratories (PTB and NPL) use a monitoring instrument. This is inserted between the source and the chamber diaphragm. The filtration of this chamber is included when obtaining the indicated half value layer in Tables 4 and 5.

At I.D., NBS and PTB the roentgen tubes are operated with a constant potential high voltage generator. At NPL two roentgen tubes cover the 80 to 290 kV range but the generators for each tube at the time of the measurement provided a pulsating potential.

A substitution method is used for the calibration of the cavity chamber at each of the laboratories. The dose rate is first determined by the national standard. The standard is then moved out of the way and the cavity chamber is accurately centered at the position previously occupied by the aperture of the free air chamber diaphragm. After determination of the ionization current in the cavity chamber it is removed and the free air chamber repositioned and the dose rate is determined again.

The dose rate for the 2 MV roentgen beam and for the cobalt 60 and cesium 137 gamma ray beams is determined by means of cavity chambers. The cavity chambers and the corrections used for the 2 MV roentgen beam calibration are described by BARNARD et coll. (1956, 1959a, 1959b). The graphite cavity chamber used for the cobalt 60 and cesium 137 gamma ray beam calibrations is described by ATTIX and RITZ (1957) and the corrections are discussed by WYCKOFF (1960). (The stopping power corrections used for these calibrations are those labeled "Bakker and Segrè" in the paper mentioned here.)

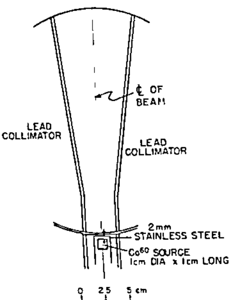



Fig 4 Cross-sectional view of 100 curie cobalt 60 source and collimator used for gamma ray cal bration The graphite chamber is positioned on the center line of the beam at a distance of approximately 1 meter from the source

The geometrical arrangement of the source and collimation for these cali brations are shown in Figs 4 and 5 Calibration of the gamma ray beams is obtained with the radiation incident at about 45 degrees to the axis of the cylindrical chamber This is necessary in order to reduce the end wall attenu ation discussed by ATTIX and RITZ

The 2 MV roentgen beam is pro- duced by electrons accelerated by a Van de Graaff generator The trans mission target is of 2 3 mm thick tungsten and the focal spot is about 0 3 mm diameter A conical aperture in a tungsten alloy collimator gives a beam of half angle about 43 The HVL of the radiation is 11 9 mm Cu Calibrations are performed at 180 cm from the target

## Results

For the calibrations obtained with free air chambers the calibration factor M of the cavity chamber is obtained from

$$M = \frac{1\ 7986\ 10^{11}}{A\ L} K \quad K_f \quad K \quad K_{sh} \quad K_l \quad K_p \quad K_h \left(\frac{1}{1-K} + K_{sc}\right) \left(\frac{T}{T}\right) \left(\frac{C}{C}\right) \frac{\left(\frac{\Delta v}{\Delta t}\right)}{\left(\frac{\Delta v}{\Delta t}\right)} \text{ r/amp min}$$

where $A$ is the area of the diaphragm in $cm^2$
$L$ is the length of the collecting electrode in cm
$K$ is the correction for air attenuation in a distance F (see Fig 2)
$K_f$ is the correction for field distortion (see Table 1)
$K$ is the correction for lack of saturation
$K$ is the correction for loss of ionization from secondary electrons [illegible] inadequate plate separation
$K$ is the correction for ionization produced by scattered photons
$K_{sh}$ is the correction (WEHRHEIM 1938) for shadowing of the coll[illegible] cable only to the PTB chamber
$K_l$ is the correction for radiation leaking into the free air chamber
$K_p$ is the correction for radiation penetration of the aperture [illegible]
$K_h$ is the correction for humidity
$T$ is the absolute temperature in the free air chamber

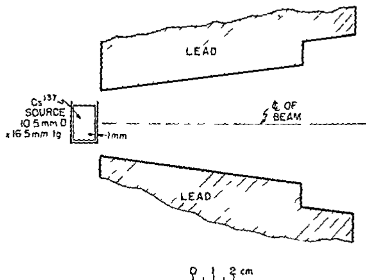



Fig 5 Cross-sectional view of 120 curie cesium 137 source and collimator used for gamma ray calibration The graphite chamber is positioned on the center line of the beam at a distance of approximately 83 cm from the source

$T$ is the absolute temperature in the cavity chamber (assumed to be the same as in the room)

$C$ is the capacitance in farads of the capacitor used for determining the charge collected from the free air chamber

$C$ is the capacitance in farads of the capacitor used for determining the charge collected from the cavity chamber

$\left(\frac{\Delta v}{\Delta t}\right)$ is the rate of change of potential in volt/sec on the capacitor used with the free air chamber and

$\left(\frac{\Delta v}{\Delta t}\right)$ is the rate of change of potential in volt/sec on the capacitor used with the cavity chamber

Values for $K_f$ are obtained by the methods outlined by WYCKOFF and ATTIX (1957) Values of $K$ are obtained from the same reference Values of $K$ used at PTB are obtained from the paper by HUBNER (1958) Each of the other three laboratories determined the values experimentally Values of $K_s$ and $K$ are obtained either from measurements in the particular laboratory (NPL NBS) or from the data reported by WYCKOFF and ATTIX The data for $K$ in this reference are corrected in accordance with the more precise values obtained by RITZ (1959) and HENRY (1961) (See correction sheet added to the WYCKOFF and ATTIX reference in 1961 ) Values of $K_k$ are obtained from the report by BARNARD ASTON and MARSH (1961) The value of $K_t$ is obtained experimentally by noting the charge collected when the diaphragm is replaced with a solid plug or by measurements with a thicker diaphragm (NPL) The value of $K_p$ is determined by computing the ratio of the radiation transmitted by the border of the aperture to that passed by the aperture

The data obtained at NBS before cavity chambers II and IX were shipped to the other laboratories are indicated in Table 2. Data obtained after they were returned to NBS are indicated in italics in the same table. The data obtained at LD, PTB and NPL, respectively, are given in Tables 3, 4 and 5. No humidity data are available for some of the calibrations. However, from the recorded temperature and the usual relative humidity encountered during the time of these measurements the estimated correction probably is not more than 0.05 to 0.02 per cent for Table 2 and about twice this for Table 3. When these data were not available these corrections have been neglected in computing the value of $M$.

At NBS the exposure time $\Delta t$ is usually the same for both the free air and the cavity chambers. At LD the value of the capacitor potential was the same for both instruments.

At NPL experience has indicated no difference in the temperature of the interior of the free air chamber and the room. For this laboratory the value of $T/T$ is 1.000.

An additional correction $k_A$ is applied at NBS because of the lack of coplanarity of the guard plates and the collector plate. Earlier measurements (RITZ 1960) indicated that $k_A = 1.0015$. Measurements made after the calibrations reported here indicated that the correction is still the same.

For the gamma ray and 2 MV roentgen calibrations the calibration factor is given by

$$M = {}^{R}/_{C} \left(\frac{\Delta v}{\Delta t}\right) \left(\frac{T}{273.2}\right) \left(\frac{760}{P}\right) k_A \qquad (2)$$

where

$R$ is the exposure dose rate at the calibration point in r/min,

$P$ is the atmospheric pressure in mm of mercury and the other symbols having the meaning previously described.

Results of such calibrations are given in Table 6.

One of the investigators (G. P. BARNARD) noted a $\pm$ 0.2 per cent variation of response with direction of incident 2 MV radiation on chamber II but none on chamber IX. No investigation for such a possible orientation dependence was conducted before the chambers left NBS but an attempt was made to verify the NPL results after the chambers were returned. In agreement with NPL no orientation dependence greater than the reproducibility (about *0.1* per cent) was observed for chamber IX with cobalt 60 gamma rays. The results for chamber II are less certain. Shortly after the chambers were returned to NBS chamber II developed an intermittent electrical short between the center electrode and the grounded aluminum tube. Radiograms indicated that the collecting electrode was not positioned on a diameter of the cavity. Forced rotation of the center pin of the BNC connector which connects directly to the collecting electrode, moves the center electrode on the surface

**Table 2**

*Data from National Bureau of Standards at the start and end of intercomparison*
*(The values from the end of the intercomparison are in italics)*

| kV | Total filtration mm | | HVL (mm Cu) | Approx dose rate (r/min) | Free air chamber corrections * | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Cu | | | $A$ | $A$ | $A_f$ | $A_p$ |
| 60 | 4 4 | 0 | 0 089 | 0 67 | $1\,013_1$ | $1\,000_1$ | 1 000 | 1 000 |
| 75 | 4 1 | 0 | 0 11 | 1 12 | $1\,011_8$ | $1\,000_8$ | 1 000 | 1 000 |
| 100 | 3 4 | 0 | 0 20 | 1 69 | $1\,009_9$ | 1 000 | 1 000 | 1 000 |
| 150 | 3 4 | 0 25 | 0 66 | 2 3 | $1\,006_4$ | $1\,001_0$ | 1 000 | 1 000 |

**Table 2** *(cont.)*

| $K$ | $K_{se}$ | Chamber | Date | $\frac{(\Delta v/\Delta t)}{(\Delta v/\Delta t)}$ | $\frac{T}{\bar{T}}$ | $k_h$ | M 10 (r/amp min) |
|---|---|---|---|---|---|---|---|
| 0.000 | 0.007 | II | 2/6/59 | 0.7576 | 1.000 | | 1.806 |
| | | | 2/13/59 | 0.7509 | 1.000 | | 1.801 |
| | | | *5/9/60* | *0.7900* | *1.000* | *1.000* | *1.802* |
| | | | *1/10/61* | *[illegible]* | *1.000* | *1.000* | *1.801* |
| | | IX | 1/18/59 | 0.7179 | 1.001 | | 1.724 |
| | | | 2/14/59 | 0.7174 | 1.001 | | 1.722 |
| | | | *5/5/60* | *0.7541* | *1.000* | *1.000* | *1.721* |
| | | | *5/9/60* | *0.7542* | *1.001* | *1.000* | *1.722* |
| | | | *1/10/61* | *7459* | *1.000* | *1.000* | *1.731* |
| 0.000 | 0.007 | II | 2/6/59 | 0.7427 | 1.000 | | 1.779 |
| | | | 2/13/59 | 0.7413 | 1.000 | | 1.775 |
| | | | *5/10/60* | *0.7784* | *1.000* | *1.000,* | *1.772* |
| | | | *1/10/61* | *0.7330* | *1.001* | *1.000* | *1.772* |
| | | IX | 1/18/59 | 0.7089 | 1.002 | | 1.700 |
| | | | 2/13/59 | 0.7061 | 1.001 | | 1.693 |
| | | | 2/14/59 | 0.7076 | 1.001 | | 1.696 |
| | | | *5/5/60* | *0.7442* | *1.000* | *1.000* | *1.695* |
| | | | *1/10/61* | *0.7032* | *1.001* | *1.000* | *1.700* |
| 0.000 | 0.006 | II | 2/6/59 | 0.7264 | 1.001 | | 1.740 |
| | | | 2/13/59 | 0.7258 | 1.000 | | 1.738 |
| | | | *5/10/60* | *0.7613* | *1.001* | *1.000* | *1.734* |
| | | | *1/10/61* | *0.7182* | *1.002* | *1.000* | *1.738* |
| | | IX | 1/18/59 | 0.6932 | 1.002 | | 1.662 |
| | | | 2/13/59 | 0.6907 | 1.001 | | 1.654 |
| | | | 2/14/59 | 0.6926 | 1.001 | | 1.659 |
| | | | *5/5/60* | *0.7 63* | *1.001* | *1.000* | *1.654* |
| | | | *1/10/61* | *0.6846* | *1.002* | *1.000* | *1.6 7* |
| 0.001 | 0.004 | II | 2/6/59 | 0.7161 | 1.001 | | 1.717 |
| | | | 2/14/59 | 0.7151 | 1.002 | | 1.716 |
| | | | *5/10/60* | *0.7523* | *1.001* | *1.000* | *1.715* |
| | | | *1/10/61* | *0.7119* | *0.999* | *1.000* | *1.719* |
| | | IX | 1/18/59 | 0.6787 | 1.002 | | 1.629 |
| | | | 2/14/59 | 0.6784 | 1.001, | | 1.626 |
| | | | *5/6/60* | *0.7112* | *1.000* | *1.000* | *1.619* |
| | | | *1/10/61* | *0.6710* | *0.999* | *1.000* | *1.619* |

**Table 2** *(cont)*

| kV | Total filtration mm Al | Cu | HVL (mm Cu) | Approx dose rate (r/min) | Free air chamber corrections * $k_a$ | $k_s$ | $k_l$ | $k_p$ |
|---|---|---|---|---|---|---|---|---|
| 200 | 5 4 | 0 52 | 1 26 | 3 6 | 1 005 | 1 $001_4$ | 1 000 | 1 000 |
| 250 | 5 4 | 1 02 | 2 17 | 4 7 | 1 $005_2$ | 1 001 | 1 000 | 1 000 |
| 250 | 5 4 | 3 15 | 3 2 | 2 4 | 1 $004_5$ | 1 001 | 1 000 | 1 000 |

* In eq 1 the value of $\frac{1\ 7986\ 10^{11}}{VL}$ $K_f\ k_c$ = 0 22750 10 for the 1959 data $\frac{C}{C}$ = 10 469 for the 1960 data $\frac{C}{C}$ = 9 9475 for the 1961 data at 60 kV $\frac{C}{C}$ = 1 0132 and for th remainder of the 1961 data $\frac{C}{C}$ = 10 558

of an imaginary small cone Apparently the axis of the collecting electrode and its connection are not the same

Measurements on the radiograms of this chamber also indicated no large differences in wall thickness such as might exist if the outer and inner sphere did not have the same center The uncertainty (0 1 to 0 2 mm) in such meas urement, however, is large enough so that this reason for orientation de

**Table 2** *(cont)*

| K | λ | Chamber | Date | $\left(\frac{\Delta v}{\Delta t}\right)_*$ / $\left(\frac{\Delta v}{\Delta t}\right)$ | $\frac{T}{T}$ | $K_h$ | M $10^{-11}$ (r/amp min) |
|---|---|---|---|---|---|---|---|
| 0 004 | 0 004 | II | 2/6/59 | 0 7200 | 1 001 | | 1 731 |
| | | | 2/14/59 | 0 7193 | 1 002 | | 1 730 |
| | | | *5/10/60* | *0 7583* | *1.001* | *1.000* | *1 73?* |
| | | | *1/10/61* | *0 7138* | *1.000,* | *1.000* | *1 728* |
| | | IX | 1/18/59 | 0 6796 | 1 003 | | 1 636 |
| | | | 2/14/59 | 0 6788 | 1 001, | | 1 632 |
| | | | *5/6/60* | *0 7118* | *1 000,* | *1 000* | *1.C74* |
| | | | *1/10/61* | *0.6716* | *1.000* | *1.000* | *1.626* |
| 0 003 | 0 003 | II | 2/6/59 | 0 7234 | 1 001 | | 1 744 |
| | | | 2/14/59 | 0 7254 | 1 002 | | 1 746 |
| | | | *5/10/60* | *0 7620* | *1.001* | *1 000,* | *1.74?* |
| | | | *1/10/61* | *0 7214* | *1 00?* | *1.000,* | *1 752* |
| | | IX | 1/18/59 | 0 6818 | 1 004 | | 1 644 |
| | | | 2/14/59 | 0 6825 | 1 001 | | 1 642 |
| | | | *5/6/60* | *0 7155* | *1 001* | *1 000* | *1 635* |
| | | | *1/10/61* | *0 6761* | *1 001* | *1.000* | *1.640* |
| 0 003 | 0 003 | II | 2/6/59 | 0 7303 | 1 001 | | 1 754 |
| | | | 2/14/59 | 0 7321 | 1 002 | | 1 759 |
| | | | *5/10/60* | *0 7713* | *1 001* | *1.000,* | *1 760* |
| | | | *1/10/61* | *0 7278* | *1 00?* | *1 000* | *1 765* |
| | | IX | 1/18/59 | 0 685? | 1 004 | | 1 650 |
| | | | 2/14/59 | 0 6860 | 1 002 | | 1 649 |
| | | | *5/6/60* | *0 7189* | *1.000* | *1 000* | *1.640* |
| | | | *1/10/61* | *0.6788* | *1 003* | *1 000* | *1.647* |

* Estimated

pendence of calibration cannot be ruled out Calibrations of chamber II at NBS indicated that the orientation dependence may be as large as reported by NPL but the reproducibility is of the same order (about 0 1 per *cent*) Such calibrations included determinations with cobalt 60 gamma rays and with 100 kV roentgen rays The latter determinations also included different orientations of the collecting electrode

**Table 3**

*Data from Laboratoire de Dosimétrie*

| kV | Added filter (mm) | | HVL (mm Cu) | Approx. dose rate (r/min) | Free air chamber corrections | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Cu | | | $K_a$ | $I$ | $P_l$ | $K_p$ |
| 60 | 1.2 | — | 0 08 | 0 36 | 1 009 | 1 001 | 1 000 | 1 000 |
| 100 | 1 8 | — | 0 2 | 0 38 | 1 007 | 1 001 | 1 000 | 1 000 |
| 150 | 1 | 0 25 | 0 65 | 1 35 | 1 005 | 1 001 | 1 000 | 1 000 |
| 200 | 1 | 0 5 | 1.2 | 2 12 | 1 004 | 1 001 | 1 000 | 1 000 |

* *The HVL in copper at 60 kV was not measured at the Laboratoire de Dosimetrie but the HVL in aluminum was determined to be 2 85 mm As this agrees very well with the HVL in aluminum (2 9 mm) determined at NPS it is assumed that the HVL in copper for 60 kV X rays is the same as that obtained at NBS*

The reason for the orientation dependence has not been definitely established at this time but care should be taken to minimize the probability of its happening in the future Radiograms of the chamber after construction will check the centering of the collector electrode The chamber could be calibrated always in the same orientation This is now the standard practice at NBS While the magnitude of the orientation dependence is probably not large it is suggested that these two precautions be observed for future intercomparisons

## Comparison of results

An examination of the results listed in Table 2 permits an evaluation of the reproducibility of the cavity chamber calibration In order to eliminate possible changes of these calibrations between the two sets, it is necessary to examine separately the data taken before and after shipment The maximum deviation of any calibration from the mean value obtained for either chamber at any one quality varies from about 0 03 to 0 3 per cent The mean value of these

Table 3 *(cont )*

| $K$ | $k_{sc}$ | Chamber | $\frac{\Delta v}{\Delta v}$ | Date | $\frac{T}{T}$ | M 10* (r/amp min) |
|---|---|---|---|---|---|---|
| 0 000 | 0 006 | II | 1 000 | 4/21/59 | 0 9953 | 1 794 |
| 0 000 | 0 004 | II | 1 000 | 4/13/59 | 0 9983 | 1 741 |
| | | | | 4/14/59 | 0 9971 | 1 737 |
| | | | | 4/15/59 | 0 9958 | 1 735 |
| | | | | 4/17/59 | 0 9980 | 1 737 |
| | | | | 4/21/59 | 0 9932 | 1 741 |
| 0 003 | 0 003 | II | 1 000 | 4/10/59 | 0 9976 | 1 715 |
| | | | | 4/14/59 | 0 9969 | 1 714 |
| | | | | 4/16/59 | 0 9986 | 1 712 |
| | | | | 4/20/59 | 0 9986 | 1 718 |
| 0 007, | 0 003 | II | 1 000 | 4/14/59 | 0 9970 | 1 728 |
| | | | | 4/15/59 | 0 9974 | 1 727 |
| | | | | 4/17/59 | 0 9969 | 1 725 |
| | | | | 4/21 59 | 0 9988 | 1 730 |

* In eq 1 the value of $\frac{1\ 7986\ 10}{4\ L}$ $K_f = 0\ 38621\ 10$ $\frac{C}{C} = 9\ 762$

deviations for all qualities for either chamber is about 0 1 per cent Similar ranges and mean values are obtained from the data in the other tables where there are sufficient data for analysis

A comparison of the two sets of data from NBS permits a determination of the long term stability of the calibration The ratio of the mean calibration factor in the first set to that in the second set for the same quality is taken as a measure of the *long term stability* For chamber II this ratio varies from about 0 997 to 1 003 for the different qualities and the mean value for all qualities is 1 000 For chamber IX the ratio varies from about 0 999 to 1 006 with a mean value of 1 003

Thus there appears to be a reproducibility uncertainty of as much as 0 3 per cent for either chamber when only a small number of measurements are available In addition there appears to be a possible orientation dependence of up to 0 2 per cent for chamber II and a drift of calibration of up to 0 3 per cent for chamber IX These factors set the maximum uncertainty of the calibration at about 0 5 per cent Thus one might expect that the lack of reproducibility

**Table 4**

*Data from the Physikalisch Technische Bundesanstalt*

| kV | Added filter (mm) | | HVL (mm Cu) | Approx. dose rate (r/min) | Free air chamber corrections | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Cu | | | $F$ | $K$ | $K_{sh}$ | $K_l$ |
| 60 | — | — | 0 083 | 0 28 | 1 021 | 1 000$_7$ | 1 001 | 1 000 |
| 75 | — | — | 0 110 | 0 58 | 1 018$_4$ | 1 000 | 1 001$_2$ | 1 000 |
| 100 | 1 0 | — | 0 197 | 1 02 | 1 014$_6$ | 1 000 | 1 001$_3$ | 1 000 |
| 150 | 1 0 | 0 13 | 0 64$_7$ | 1 15 | 1 011 | 1 000 | 1 001 | 1 000 |
| 200 | 1 0 | 0 26 | 1 20 | 1 00 | 1 010 | 1 000 | 1 001$_7$ | 1 000 |
| 200 | 1 0 | 0 26 | 1 20$_5$ | 1 00 | 1 010 | 1 000$_5$ | 1 001 | 1 000 |
| 250 | 1 0 | 0 72 | 2 11 | 1 18 | 1 009 | 1 000 | 1 001$_2$ | 1 000 |
| 250 | 1 0 | 3 0 | 3 13 | 1 12 | 1 008 | 1 000 | 1 001 | 1 000 |
| 250 | 1 0 | 3 0 | 3 13 | 1 12 | 1 008 | 1 000 | 1 001$_8$ | 1 000 |
| 300 | 1 0 | 4 0 | 3 95 | 1 10 | 1 008 | 1 000 | 1 001$_2$ | 1 000 |
| 350 | 1 0 | 6 0 | 4 74 | 1 10 | 1 008 | 1 000 | 1 001 | 0 9918 |

* Inherent filtration about 4 mm Al

** In eq 1 the value of $\frac{1\ 7986\ 10}{A\ L}$ $F_f = 0\ 091231\ 10$

of the calibration of either chamber at any laboratory for any quality should not exceed about 0 5 per cent

As the data from the four laboratories are not all obtained for the same qualities it is necessary to interpolate in order to compare the results The calibration factor obtained for the two chambers at the four laboratories are plotted against the half value layer (HVL) of the radiation in Figs 6 and 7 The vertical line for each NBS calibration indicates the range of values obtained while the circle indicates the mean value For clarity only the mean values are plotted for the other laboratories A smooth curve is drawn through the

**Table 4** *(cont.)*

| $K_p$ | $\frac{1}{1-K\ K_{se}}$ | Chamber | Date | $\left(\frac{C}{C}\right)\frac{\left(\frac{\Delta v}{\Delta t}\right)}{\left(\frac{\Delta v}{\Delta t}\right)}$ | $\frac{T}{T_e}$ | $k_h$ | M $10^{-11}$ (r/amp min) |
|---|---|---|---|---|---|---|---|
| 1.000 | 0.9896 | II | 6/8/59 | 19.499 | 1.001 | 1.0017 | 1.808 |
| | | IX | 6/8/59 | 18.685 | 1.001 | | 1.732 |
| 1.000 | 0.9899 | II | 6/1/59 | 19.248 | 0.999 | 1.0013 | 1.773 |
| | | IX | 6/1/59 | 18.418 | 0.998 | | 1.696 |
| 1.000 | 0.9913 | II | 5/28/59 | 18.930 | 1.000 | 1.0011 | 1.743 |
| | | IX | 5/28/59 | 18.016 | 1.001 | | 1.660 |
| 1.000 | 0.9933 | II | 6/3/59 | 18.629 | 1.000 | 1.0012** | 1.713 |
| | | IX | 6/3/59 | 17.726 | 1.001 | | 1.630 |
| 1.000 | 0.9943 | II | 6/2/59 | 18.716 | 1.002 | 1.0011 | 1.723 |
| | | IX | 6/2/59 | 17.654 | 1.002 | | 1.625 |
| 1.000 | 0.9943 | II | 6/11/59 | 18.756 | 1.002 | 1.0011 | 1.727 |
| | | IX | 6/11/59 | 17.698 | 1.001 | | 1.628 |
| 1.000 | 0.9954 | II | 5/29/59 | 18.918 | 1.001 | 1.0008** | 1.740 |
| | | IX | 5/29/59 | 17.735 | 1.001 | | 1.632 |
| 1.000 | 0.9940 | II | 6/4/59 | 19.051 | 1.000 | 1.0005 | 1.748 |
| | | IX | 6/4/59 | 17.826 | 1.001 | | 1.637 |
| 1.000 | 0.9940 | II | 10/15/59 | 19.027 | 1.002 | 1.0004 | 1.748 |
| | | IX | 10/15/59 | 17.888 | 0.999 | | 1.638 |
| 1.000 | 0.9963 | II | 10/13/59 | 19.079 | 0.999 | 1.0003 | 1.752 |
| | | IX | 10/13/59 | 17.931 | 1.000 | | 1.647 |
| 0.9983 | 0.9973 | II | 10/14/59 | 19.368 | 0.999 | 1.0003 | 1.763 |
| | | IX | 10/14/59 | 18.113 | 1.001 | | 1.650 |

** Estimated

NBS roentgen data points. The large value for the softer qualities results from the large wall attenuation which decreases for the harder radiations. The rise beyond the minimum is due to the decrease of the photoelectric effect in the aluminum center electrode.

The deviation of the calibration factors obtained at LD, NPL and PTB from the smooth curve through the NBS results are listed in Table 7. Column 3 of that table gives the deviations for chamber II, column 4 for chamber IX, and column 5 the mean value for the two chambers at each of the qualities. The maximum difference between columns 3 and 4 is 0.9 per cent for one

**Table 5**

*Data from National Physical Laboratory*

| kV | Added filter * (mm) | | HVL (mm Cu) | Approx dose rate (r/min) | Free air chamber corrections | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Cu | | | $J$ | $K$ | $K_p$ | $A_t$ |
| 80 | — | — | 0 103 | 2 1 | 1 023 | 1 007 | 1 000 | 1 000$_6$ |
| 125 | 1 0 | — | 0 200 | 4 3 | 1 015 | 1 004$_5$ | 1 000 | 1 000 |
| 125 | 1 0 | 0 05 | 0 250 | 3 4 | 1 014 | 1 003 | 1 000 | 1 000 |
| 145 | 1 0 | 0.25 | 0 50 | 2 7 | 1 011$_5$ | 1 002 | 1 000 | 1 000 |
| 180 | — | — | 1 02 | 3 4 | 1 010$_5$ | 1 003 | 1 000 | 1 000 |
| 250 | 1 0 | 0 1 | 1 53 | 5 7 | 1 009 | 1 005 | 1 000 | 0 999 |
| 290 | 1 0 | 0 63 | 2 19 | 6 4 | 1 008 | 1 006$_5$ | 1 000 | 0 998 |
| 250 | 1 0 | 1 9 | 2 55 | 2 6 | 1 008$_5$ | 1 002 | 1 000 | 0 998 |
| 290 | 1 0 | 4 0 | 3 40 | 2 5 | 1 007 | 1 002 | 1 000 | 0 995 |

* From 80 to 145 kV the tube had an inherent filtration equivalent to about 0 095 mm Cu and at higher voltages to about 1 1 mm Cu. The monitor provided a permanent additional filtration of 8 mm perspex.

quality but the next highest difference is 0 6 per cent and the remainder are 0 4 per cent or less These differences are consistent with the expected reproducibility noted above

Table 5 *(cont.)*

| | | Cavity chamber number | Date of measurements | $P$** | $k_h$ | M 10³ (r/amp min) |
|---|---|---|---|---|---|---|
| $k$ | $k$ | | | | | |
| 0 000 | 0 006 | II | 12/8/59 | 1 7602 | 1 001 | 1 796 |
| | | II | 12/14/59 | 1 7693 | 1 001, | 1 805 |
| | | IX | 1/16/60 | 1 6774 | 1 001 | 1 711 |
| | | IX | 1/8/60 | 1 6811 | 1 000 | 1 715 |
| 0 000 | 0 006 | IX | 1/7/60 | 1 6334 | 1 000 | 1 663 |
| | | IX | 1/8/60 | 1 6445 | 1 000 | 1 669 |
| 0 000 | 0 006 | II | 12/9/59 | 1 7066 | 1 000 | 1 728 |
| | | II | 12/15/59 | 1 7050 | 1 001 | 1 727 |
| 0 000 | 0 006, | II | 12/9/59 | 1 6846 | 1 000 | 1 701 |
| | | II | 12/14/59 | 1 6989 | 1 000 | 1 715 |
| | | II | 12/15/59 | 1 6962 | 1 000 | 1 713 |
| | | IX | 1/7/60 | 1 6104 | 1 000 | 1 626 |
| | | IX | 1/11/60 | 1 6138 | 1 000 | 1 629 |
| 0 000 | 0 005 | II | 12/9/59 | 1 7007 | 1 000 | 1 718 |
| | | II | 12/11/59 | 1 7036 | 1 000 | 1 721 |
| | | IX | 12/31/59 | 1 6124 | 1 000 | 1 628 |
| | | IX | 1/11/60 | 1 6109 | 1 000 | 1 627 |
| 0 001 | 0 005 | II | 1/27/60 | 1 7291 | 1 000 | 1 750 |
| | | II | 1/28/60 | 1 7293 | 1 000 | 1 750 |
| 0 002 | 0 004 | II | 12/22/59 | 1 7466 | 1 000 | 1 768 |
| | | II | 1/25/60 | 1 7376 | 1 000 | 1 758 |
| | | IX | 1/4/60 | 1 6341 | 1 000 | 1 654 |
| | | IX | 1/18/60 | 1 6338 | 1 000 | 1 653 |
| 0 002 | 0 004 | II | 12/10/59 | 1 7431 | 1 000 | 1 757 |
| | | II | 12/16/59 | 1 7421 | 1 000 | 1 756 |
| 0 001 | 0 004 | II | 12/10/59 | 1 7498 | 1 000 | 1 758 |
| | | II | 12/11/59 | 1 7565 | 1 000 | 1 764 |
| | | IX | 1/20/60 | 1 6553 | 1 000 | 1 663 |
| | | IX | 1/21/60 | 1 6531 | 1 000 | 1 660 |

* $P = \frac{1\ 7986\ 10}{A\ L}\left(\frac{C}{C}\right)\frac{\left(\frac{\Delta I}{\Delta t}\right)}{\left(\frac{\Delta v}{\Delta t}\right)}$

It is noted that the average calibration factors obtained at NPL tend to be larger than those obtained at NBS and those at PTB seem to be lower especially at the harder qualities Those at LD are in close agreement but

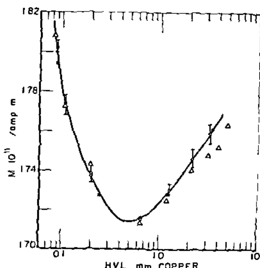



Fig 6 Average calibration factors for chamber II obtained at the four laboratories for the various qualities □ = LD ○ = NBS ● = NPL △ = PTB The vertical line through each NBS point gives the range of values obtained

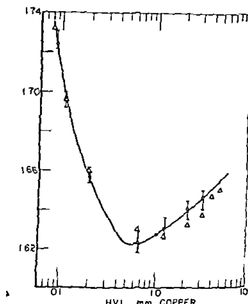



Fig 7 Average calibration factors for chamber IX obtained at three laboratories for the various qualities ○ = NBS ● = NPL, △ = PTB The vertical line through each NBS point gives the range of values obtained

cover only a limited range of qualities There has been no previous intercomparison between NBS and PTB but the previous indirect intercomparison between LD and NBS and the previous direct intercomparisons between NPL and NBS gave results similar to the present ones The last column of Table 7 indicates the deviations previously obtained (Allisy et coll 1957, and Aston and Attix 1956) for approximately the indicated qualities It is seen that these values differ from those obtained in the present intercomparisons by not more than the expected amount (0 5 per cent) While the previous NBS NPL intercomparisons were obtained with a d c generator for the roentgen tube, the present results are obtained with a pulsating potential at NPL and a d c generator at NBS The good agreement between columns 5 and 6 indicate that the effect of this different wave form is not greater than the possible lack of reproducibility, 0 5 per cent

For the previous NBS NPL intercomparison the dose rates and target diaphragm distances were the same for both chambers and determinations were made at the same collecting field strengths During the present measurements, the dose rates target diaphragm distances and field strengths were all different at the two laboratories The saturation corrections $K$ were

**Table 6**

*High energy calibrations*

| Source | HVL (mm Cu) | Chamber | Date | $M$ 10$^{-11}$ (r/amp min) |
|---|---|---|---|---|
| Co$^{60}$ (NBS) | 14 7 | II | 2/9/59 | 1 780 |
| | | IX | 2/9/59 | 1 663 |
| Cs$^{137}$ (NBS) | 10 5 | II | 2/10/59 | 1 788 |
| | | IX | 2/11/59 | 1 680 |
| 2 MV roentgen rays (NPL) | 11 9 | II | 2/16/60 | 1 774 |
| | | | 2/19/60 | 1 771 |
| | | | 3/4/60 | 1 770 |
| | | IX | 2/16/60 | 1 650 |
| | | | 3/3/60 | 1 648 |
| | | | 3/4/60 | 1 649 |
| Co$^{60}$ (NBS) | 14 7 | II | 5/19/60 | 1 793 |
| | | | 5/19/60 | 1 774 |
| | | | 5/20/60 | 1 773 |
| | | | 1/6/61 | 1 775 |
| | | IX | 5/19/60 | 1 650 |
| | | | 5/30/60 | 1 655 |
| | | | 1/6/61 | 1 659 |
| Cs$^{137}$ (NBS) | 10 5 | II | 5/19/60 | 1 794 |
| | | | 5/29/60 | 1 799 |
| | | IX | 5/16/60 | 1 666 |
| | | | 5/20/60 | 1 667 |
| | | | 5/29/60 | 1 673 |

determined at each laboratory under the conditions used at that laboratory Further investigations are needed to assure that these are consistent

As noted earlier the NPL results tend to be higher than NBS and PTB lower for the harder qualities Moreover the present results for NPL are in moderately good agreement with those obtained earlier Good agreement in the area of diaphragms and in the value of the capacitance used for current measurement (ICRU Report 1959) seem to rule out these factors as contributing to these differences In any case because both the NPL and PTB chambers are larger than the NBS chamber the differences cannot be attributed to a simple function of chamber size Perhaps detailed redetermination of the correction factors will be necessary in order to obtain a reason for these differences

The measurements with gamma rays and 2 MV roentgen rays give less useful intercomparison The large spread in the NBS calibration factors and the large difference in the spectra of the roentgen and gamma ray sources make a comparison difficult In view of these difficulties the intercomparisons seem reasonable

**Table 7**

*Comparison of calibration factors—deviation of calibration factor from NBS (per cent)*

| HVL (mm Cu) | Lab | Chamber II | Chamber IX | Av | Previous** |
|---|---|---|---|---|---|
| 0 083 | PTB | −0 1 | −0 1 | −0 1 | |
| 0 089 | LD | −0 4 | — | −0 4 | 0 0 |
| 0 103 | NPL | +0 8 | +0 4 | +0 6 | +0 5 |
| 0 11 | PTB | 0 0 | 0 0 | 0 0 | |
| 0 197 | PTB | +0 3 | +0 2 | +0 3 | |
| 0 20 | LD | +0 1 | — | +0 1 | +0 1 |
| 0 20 | NPL | — | +0 6 | +0 6 | +0 4 |
| 0 25 | NPL | 0 0 | — | 0 0 | +0 4 |
| 0 50 | NPL | −0 2 | +0 2 | 0 0 | +0 3 |
| 0 64$_7$ | PTB | −0 2 | +0 4 | +0 1 | |
| 0 65 | LD | 0 0 | — | 0 0 | +0 4 |
| 1 02 | NPL | −0 3 | +0 0 | −0 2 | +0 3 |
| 1 2 | LD | −0 1 | — | −0 1 | −0 1 |
| 1 20 | PTB | −0 2 | −0 2 | −0 2 | |
| 1 53 | NPL | +0 8 | — | +0 8 | +0 4 |
| 2 11 | PTB | −0 3 | −0 4 | −0 4 | |
| 2 19 | NPL | +1 0 | +0 8 | +0 9 | +0 5 |
| 2 55 | NPL | +0 2 | — | +0 2 | |
| 3 13 | PTB | −0 6 | −0 5 | −0 6 | |
| 3 4 | NPL | 0 0 | +0 9 | +0 5 | |
| 3 95* | PTB | −0 8 | −0 2 | −0 5 | |
| 4 74* | PTB | −0 6 | −0 3 | −0 5 | |

* Deviations uncertain at this quality as an extrapolation of NBS data is involved
** For approximately the indicated HVL

## Conclusions

Indirect intercomparisons of calibrations of ionization chambers for exposure dose measurements in roentgens have been completed between the national standards of France Germany U K , and U S A with an estimated maximum uncertainty of about 0 5 per cent This is somewhat larger than that assigned to direct comparisons (ASTON and ATTIX 1957) This large uncertainty can probably be reduced by a factor of about 2 by (1) assuring that there is no drift in calibration before the intercomparison is attempted, (2) radiographs of the chambers before use to see that they are as symmetrical as possible, and (3) always calibrating the instrument in a fixed orientation Under these conditions such indirect intercomparisons should be almost as accurate as the direct ones

The present calibrations agree with those obtained earlier between three of the laboratories to within the expected uncertainty, 0 5 per cent, also the

calibrations at PTB agree with those at NBS to within 0 6 per cent However the results from NPL and PTB disagree by slightly more than one per cent for nearly the same quality of the harder radiations A detailed redetermination of some of the correction factors may be needed to remove this discrepancy

**Acknowledgement**

The measurements at NPL were mostly made by Mr A R S Marsh and Mr J E Woodall Many of the measurements at NBS were made by Mr L DeLaVergne and Mr J T Weaver The work described above has been carried out as part of the research programs of the several laboratories and this paper is published by permission of their directors

## SUMMARY

A pair of cavity ionization chambers has been circulated to the national laboratories of France Germany U K and U S A for calibration with roentgen and gamma rays The difference of their calibrations with a given quality of radiation is taken as a measure of the disagreement of the national standards The results obtained agree with some earlier direct comparisons to within the expected uncertainty of these measurements — about 0 5 per cent

## ZUSAMMENFASSUNG

Ein Paar Hohlraumsionisationskammern haben zum Zweck der Kalibrierung in den staat lichen Laboratorien von Frankreich Deutschland U K und U S A zirkuliert Die Differenz der Kalibrierungsfaktoren bei einer gegebenen Strahlenqualität wird als Mass fur die Abweichungen zwischen den nationalen Standardmethoden angenommen Die erhaltenen Resul tate stimmen mit einigen fruheren direkten Vergleichen innerhalb einer Fehlergrenze von ca 0 5 % uberein

## RÉSUMÉ

Les auteurs ont envoyé aux laboratoires nationaux d Allemagne de France du Royaume Uni et des U S A deux chambres d ionisation à cavité pour étalonnage avec les rayons roent gen et gamma La différence d étalonnage avec une qualité donnée de rayonnement est considérée comme une mesure de la discordance des étalons nationaux Les résultats obtenus concordent avec certaines comparaisons directes préalables dans l intervalle d incertitude prévisible de ces mesures environ 0 5 pour cent

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# BOOK REVIEWS

KÜNSTLICHE RADIOAKTIVE ISOTOPE IN PHYSIOLOGIE DIAGNOSTIK UND THERAPIE 2 Auflage Band I und II Herausgegeben von H Schwiegk und F Turba 2 575 Seiten und 759 Abbildungen Springer Verlag Berlin 1961 Price DM 398

The rapid increase in the use of radioisotopes for the most varied purposes in the medical sciences is well reflected in the fact that the second edition of the well known handbook of SCHWIEGK has grown to more than double the size of the first edition It contains contributions from 83 authors mostly German and American writing in their respective languages one chapter is in French About 330 of the 2 575 pages contain lists of references while the subject index fills 270 pages It is clearly impossible within a reasonable space to review in detail a work such as this and there is probably no single person in the world able critically to judge all parts of so varied a subject matter The present reviewer can claim competence only within small realms of the subjects treated

The first volume begins with a long chapter on general methods for detecting radioisotopes although without any detailed treatment of the electronic instruments in use and a still longer one on the different radioisotopes and the preparation of various compounds and samples for measurement There are chapters on autoradiography radiobiology radiation protection and the construction and equipment of nuclear medicine laboratories

A few chapters on general aspects on the use of radioisotopes in biochemistry physiology etc are followed by a number of chapters with detailed treatment of various special problems

The second volume begins with chapters on several of the most important elements and their radioisotopes Very little information is however given on half lives and radiation properties The chapter on iron describes in detail the normal and pathologic metabolism of the element and hematologic applications of radio-iron

Other chapters concern muscle and nerve physiology various metabolic studies and applications of radioisotopes in bacteriology virology and immunology Some of the chapters that follow have more direct diagnostic interest (circulation research tumour diagnostics thyroid function studies the biochemistry of vitamin B12)

The last chapters are concerned with therapeutic uses (tumour therapy hematology thyroid therapy) Uses of radioisotopes in sealed containers for internal or external irradiation including telegamma therapy are also described though relatively briefly A chapter on the therapeutic use of high energy heavy ions falls outside the scope of the book as defined in its title as in the diagnostic part do the references to uses of stable isotopes

As far as the reviewer can judge the editors and the authors have done a good job and no cause for any major criticism has been found Several duplications are of course unavoidable when different authors treat closely related subjects but they seem to be innocuous and some times even useful

The work may be considered indispensable to general medical libraries and to radiological and biophysical institutes Many research workers will also find it worth its relatively high price even though they ma have practical use of only a fraction of its contents

*Sven Benner*

THE INITIAL EFFECTS OF IONIZING RADIATIONS ON CELLS A Symposium held in Moscow October 1960 Edited by R J C Harris 367 pages 129 illustrations and 24 tables Academic Press London 1962 Price 75 sh

These are the proceedings of a Symposium in Moscow in the autumn of 1960 supported by UNESCO IAEA and the Academy of Sciences USSR

The word initial is not to be taken literally since irradiation effects that become apparent days or even weeks after the irradiation were also discussed All the usual subjects of radiation biology were covered at the meeting

The particular interest in this symposium lies in the fact that a substantial presentation of Soviet radiobiology becomes available in English nearly fifty per cent of the contributions being from Soviet scientists There were many interesting communications The material in some of the Russian papers was evidently condensed from years of work and references about interesting details are sometimes made to original publications in the Russian language

Of the papers that seem to present new lines of research and new technical ideas may be mentioned FRANK s studies on rhythmic changes in oxydative processes A micropolarographic device was developed to study these phenomena MEISSEL et alii have applied fluorescence microscopy to the study of irradiation effects on nucleic acids and proteins

The symposium was concluded by a general discussion on topics of particular interest selected from the material presented in the individual papers

*A Forssberg*

FUNDAMENTALS OF RADIOBIOLOGY By Z M Bacq and Peter Alexander Second completely revised edition 555 pages 150 illustrations and 81 tables Pergamon Press Oxford 1962 Price 70 sh

This well known book now appears in the International Series of Monographs on Pure and Applied Biology in what is virtually an entirely revised form of the first edition The great amount of experimental work that has been done in the last decade is at once apparent from a perusal of the text Radiation biology in its present stage encompasses large tracts of the sciences of chemistry and biology and also needs a fair knowledge of the fundamentals of physics A survey of radiation biology is certainly a taxing enterprise for two authors although a combination of a physics chemist and a physiologist probably comes closest to the ideal combination The selection of the material must nevertheless to some extent *reflect* their interests and scientific fields particularly as it is virtually impossible to cover the whole material in some 500 pages To quote the preface This is a survey and not a monograph We have selected certain investigations from the enormous mass of published material

Subjects such as the radiation chemistry of macromolecules and some parts of mammalian radiobiology e g the biochemistry physiology and pathology of the irradiated body are comprehensively treated and the same applies to protection The rapid development in the important field of radiation genetics is outlined in a few pages but with references as in other instances to modern reviews The book is written in a vivid and entertaining way which reflects the enthusiasms of the authors and makes for easy reading The personal views of the authors in many controversial questions e g the merits of the physical target theory in radiation biology are clearly expressed

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# ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK, FINLAND, NORWAY AND SWEDEN

| Vol 1 | New series | 1963 |
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| Fasc 2 | THERAPY PHYSICS BIOLOGY | April |


## VI SYMPOSIUM NEURORADIOLOGICUM ROMA

18—22 September 1961

## THERAPY & BIOLOGY SECTIONS

The titles of some of the papers read at the symposium but not submitted for publication in Acta Radiologica are included in the table of contents given below

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amounts sufficient to destroy small interior areas of the brain It may be that different methods will be applicable to different parts of the nervous system We have applied our efforts to the goal of destruction of the ventrolateral nucleus of the human thalamus for the treatment of dyskinesia

Some understanding of the unpredictable results of the various methods can be achieved by considering the physical nature of the area as has been stated by ARONOW Thalamic nuclear masses are relatively well vascularized The vascular fluid channels make the convection of heat variable and complex, electrical properties irregular, and mechanical punctures particularly if repeated fraught with danger of hemorrhage Also the brain tissue is a poor conductor of heat and the fluids of the region when heated to steam and gas make irregularities in the size and shape especially in larger lesions Gray matter also has a higher resistance to temperature than the white matter of the nearby internal capsule Because of the lower threshold of the capsule it may be affected before the nuclear masses are completely destroyed Another variable circumstance of this particular region and the distribution of some forms of energy is the nearby presence of either air filled or fluid filled ventricles In either case these ventricles affect the distribution of heat loss of heat or electrical change The rate of change brought about by these methods (i e rapidity of destruction) must be considered in relation to the shock to the nervous system and the effects of increasing the surrounding edema or other partial damage in nearby regions

Ionizing radiation was investigated to achieve circumscribed lesions because it lacks accessory disruptive effects and because of the sharp falloff in radiation of beta sources BOYESEN & CAMPBELL have reported lesions resulting from yttrium 90 beads in the caudate nucleus of animals However we wished to create larger lesions of at least 1 cm in diameter from a single source Also it was necessary to examine the effects in the thalamus since there are regional differences in radiation sensitivity These authors have expressed a sensitivity spectrum of the structures in this region which would be favorable for this type of energy The order of sensitivity they found was that astrocytes were the most sensitive to radiation next microglia then neurons and finally blood vessels and myelin are the most resistant A question which arises is the possible carcinogenic nature of radiation Long experience with external radiation therapy has failed to result in any verified case of glial tumor induction Beta rays are believed to affect brain tissue by the common ionization in both of these methods The risk seems small

Macrospheres of 1 2 mm in diameter containing pure beta emitting isotype yttrium 90 oxide are prepared by Brookhaven National Laboratory and shipped by air weekly to the University of California Medical Center in Los Angeles The method of preparation has been described by GINELL & DOERING These beads are readily available relatively inexpensive and of sufficient activity to be usable for a number of days after delivery

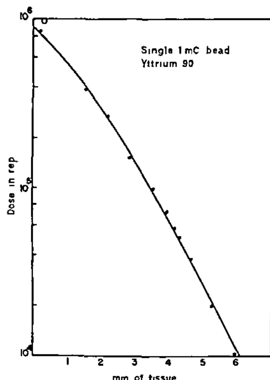



Fig 1 Film pack dosimetry curve for 1 mC yttrium 90 oxide bead calculated for 64 hours (T 1/2)

Yttrium 90 has 2 54 days half life and a maximum energy of 2 18 MeV Beta radiation has a limited range in tissue and hence there are no complicating features of distant effects The low specific gravity of the ceramic matrix in which the yttrium is suspended raises the efficiency of delivery of the total dose as compared with dense metallic sources because of the lower self absorption These yttrium 90 macrospheres are used in this medical center for transsphenoidal stereotaxic hypophysectomy as well as the procedure described in this article

From previous experience in thalamic surgery for dyskinesia it has seemed evident to us that to achieve maximum benefit in relief of various involuntary movements improvement in tone and in gait that a spherical lesion of about 7 to 10 mm *in diameter well placed in the* nuclei ventro orales anterior and posterior of the thalamus is ideal This conclusion is mainly based on observations of patients with Parkinsonism but may be true of other disorders as well

The structures critical to destroy permanently appear to be the nuclei ventro orales anterior and posterior of the thalamus With the atlas of the human brain edited by SCHALTENBRAND & BAILEY as a guide, a hypothetical lesion was measured which would involve these nuclear complexes completely A lesion placed at 12 mm from the midline in the center of these nuclei would have to be 1 cm in width 1 cm in height and 1 2 cm in length *This volume* would involve the thalamocapsular junction region which appears to be important to achieve a maximum beneficial effect Portions of other nuclei would be partly involved, including nucleus ventro oralis internus, nucleus ventro intermedius internus, nucleus medianum

The possibilities of yttrium 90 oxide spheres to involve such a volume was then investigated The film pack method of FRIETAG et coll was used for dosimetry studies Dupont 555 film was employed, with paper spacer to simulate tissue density These results reveal that radiation from a single 1 millicurie bead for a calculated time of 64 hours would give a dose of *10 000 rep at 6 mm*

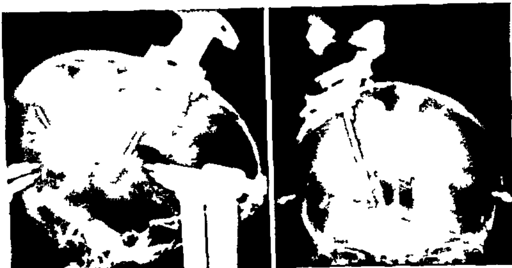


Fig 2 Concentric ring stimulating the electrode in the thalamic nuclei

The abrupt falloff in dose rate as shown in Fig 1 is characteristic of beta emitters This characteristic is ideal for producing a discrete lesion in tissue and the discreteness is further enhanced by the spherical shape and size of yttrium 90 beads The size of the lesion can be varied according to the initial activity of the bead and the length of time it is left in place The maximum penetration for yttrium 90 beta particles in tissue is 10 mm but beyond 6 mm a lethal tissue dose cannot be achieved because of marked absorption Seventy per cent of the dose is delivered in 3 days Therefore the rate of tissue destruction is considerably slower than by other methods and possibly allows collateral circulation to develop and produces less local edema

## Preliminary study of lesions in animals

Twenty one mongrel dogs of medium size had implantation of a single yttrium 90 bead in each area under general anesthesia by the stereotaxic method of LIM LIU & MOFFITT The activity of the individual beads varied from 0 85 mC to 1 9 mC The macrospheres were left in place for varying lengths of time up to 20 days The age of lesions before sacrifice of the dog was varied up to 5 months All figures quoted for the size of lesions have not been corrected for shrinkage of the formalin fixation

In the first series of experiments the beads were implanted as free bodies in the brain tissue Radiation activity of the sources varied from 1 5 to 1 9 mC each These animals each were sacrificed after anesthetization and formalin perfusion at intervals of 2 days 6 days and 141 days, and two animals at 170



Fig 3 Fixation bead holder and yttrium 90 oxide bead in the human thalamus

days Lesions in the thalamus in these animals were found to be irregular, most commonly being pear shaped This shape of the lesion was a result of 3 to 4 mm inferior migration of the bead One animal with 3 beads inserted as a cluster in white matter had a migration of the cluster of 2 5 cm An explanation of this process appears to be that beads of this activity produce a small zone of liquefaction necrosis in the immediate area Edema or hemorrhage might also displace them It was concluded that a fixation device for the bead is necessary to provide control of position and size of lesion

Twelve animals were prepared using a loop cannula for fixation Two small wire loops soldered into No 18 stainless steel tubing provided a carrier for the yttrium bead and this complex was fixed by a plastic plate screwed into the calvarium The plastic plate was drilled and the loop cannula securely fixed into its perforation with Kadon○ and then the protruding end above the surface severed The scalp was closed over this

In this series of animals the bead activity varied from 0 9 to 1 5 mC The animals were divided into two groups, group A to show the histologic reaction up to 20 days, group B to show chronic lesions at 3 to 6 months Group A consisted of 3 animals in which the extent of the acute reaction was studied as a result of the bead being in place 1 day 6 days 20 days (± 3 hours) In group B of 9 animals with chronic lesions, the bead remained for a duration of 1, 2, 3, 5, 8 12 days (± 3 hours)

Regardless of the radiation activity of a bead or its duration in place in the various phases of development of histologic changes in the lesions, it was found that the maximum swelling was at 20 days and thereafter there was a contraction of the lesion into gliosis When the bead was fixed in this manner any lesion in the area of absolute destruction was spherical Because of the decay in activity of yttrium, leaving the bead in place after 6 days does not increase the volume of the lesion

After a lesion has aged more than 20 days it becomes progressively smaller and more irregular in configuration because of shrinkage and gliosis however, the absolute destruction of the thalamic nuclear groups remains the same

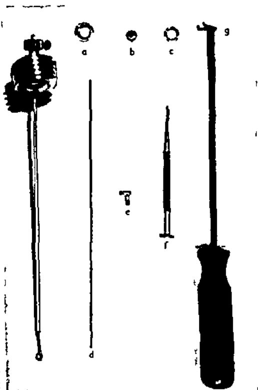



Fig 4 The assembled fixation apparatus is seen to the left a) Threaded cylinder to be screwed into a 8 mm burr hole b) Perforated metallic ball c) Fixation ring d) Stainless steel bead holder e) Set screw collar f) Jeweler s screw driver g) Screw driver for fixation ring

The maximum volume of complete destruction produced by any fixed yttrium 90 bead used and at greatest duration in place was a spherical lesion of 12 mm in diameter Fixed beads will produce circumscribed spherical lesions showing a small zone of coagulation necrosis a ring of capillary diapedesis and a small irregular zone of edema and partial damage Smaller lesions can be produced by shortening the duration of time that the bead is in place or by employing a bead of less activity

The histologic changes of a maximum lesion at 20 days are illustrated as an example In this lesion if we consider that it has a radius from the central point there is a zone 4 to 5 mm wide in which there are varying degrees of necrotic liquefaction coagulation necrosis and fibrin A few intact neurons and astrocytic nuclei may be seen even toward the center of the lesion but they do not appear viable Some polymorphonuclear, mononuclear and lymphocytic cells are seen as well as some gitter cells Around this there is a striking ring about 1 to 1 5 mm wide of a layer of diapedesis of red cells necrosis hyaline degeneration of the media and intima of blood vessels Outside this ring there is a fairly sharply defined rim 1 to 1 5 mm wide, characterized by the presence of blood vessels with proliferated intima and marked infiltration

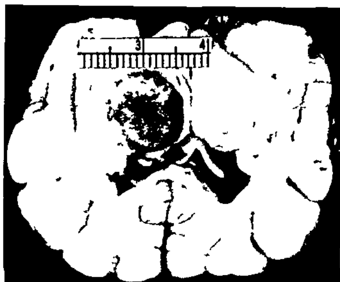



Fig 5 Lesion produced by an yttrium 90 oxide bead of 1 4 mC activity left in place in the thalamus of the dog for 6 days The dog was sacrificed at 14 days to show the early reaction

of inflammatory cells In the remaining periphery, small pseudopods of irregular shape and representative of edema are seen The edema causes some diminution in the size of the ventricular cavity but not enough to cause a shift even in the small brain of the dog More extensive exposition of the quantitative effects and the histologic reactions will be published in the near future

## Clinical application

Since October 1960, 13 patients with dyskinesia have had yttrium 90 thalamatomy Eleven patients suffered from either post encephalitic Parkinsonism or paralysis agitans 2 patients had dystonia musculorum deformans and one had post traumatic cerebellar tremor disorder Patients selected for this operation were in general severely disabled and by current standards generally used, were considered either borderline or ineligible for the ci devant alcohol injection (Cooper & Bravo) treatment used at this institution It was hoped that these radiation lesions, being highly circumscribed and controlable in size by withdrawal of the bead, would assist in rehabilitating a borderline group of cases as well as to give an evaluation of this form of treatment

*Surgical procedure* Anatomical landmarks to locate the site of the lesion are delineated by an encephalogram during which the patient s head is fixed in a Lee model 215 head and cassette holder In sole instances in which the



Fig 6 Histologic preparation of a lesion at 14 days 1 25 mC yttrium 90 oxide macrosphere left in place for 6 days

posterior part of the third ventricle was not satisfactorily seen a small amount of Pantopaque© was injected via a small catheter directed to the foramen of Monro The ventricular landmarks have been the posterior margin of the foramen of Monro the anterior and posterior commissures the habenular commissure and the pineal body In lateral roentgenograms proportions were used consisting of mid foraminal pineal line (COOPER & BRAVO) and mid antero posterior commissure axis with mid thalamic height (TALAIRACH et coll ) Our tube film distances were 36 inches giving an enlargement factor of approximately 20 % for antero-posterior and 10 % for lateral views In the antero posterior films the corrected distance from the midline third ventricle was 12 mm however in cases of atrophy it was altered further laterally References used for landmarks were the human atlas of TALAIRACH et coll , and SCHALTENBRAND & BAILEY Permanent and polaroid films have been employed The Rand Wells stereotaxic instrument with sagittal and coronal arcs was used to direct the electrode and cannula

Further identification of the nucleus ventrales lateralis of the thalamus by electrophysiological means as well as these anatomical landmarks is important This anatomical precaution is necessary because of the normal variations of these structures variations from pathological alterations and variations even from side to side in the same patient as has been well documented by BRIERLY & BECK

After a 10 mm burr hole has been made 3 5 cm from the midline at the level of the coronal suture the dura mater and cortical surface at the site are opened A tap is used to create threads in the burr hole to accept a small ball and a socket fixation device used later to fix the yttrium cannula With the stereotaxic device a Talairach multiple concentric ring electrode is then lowered to the anatomical target Sterile scalp as well as electromyographic electrodes in the limb muscles are then applied to the patient Stimuli are delivered to the depth electrode with a Grass 4S type stimulator with isolation unit Single or repetitive trains of square wave form stimuli with parameters varying from




Fig 7 Irregularly shaped lesions seen at 7 days produced by 0 95 mC activity and without fixation of the macrospheres

1 to 50 cps duration 1 msec for low frequency and 0 5 msec for high frequency The voltage and duration of stimulation have varied from 3 to 15 volts, and 5 to 10 seconds respectively, depending on responses seen in the electro-encephalogram monitoring oscilloscopes and the alert patient The electrophysiological responses identifying this area have been reported by RAND and CRANDALL In short they consist of (1) suppression or augmentation of tremor and rigidity, (2) correlation of electrophysiologic recordings of such phenomena as recruitment and evoked potentials with tremor suppression or augmentation as shown in the electro encephalogram, cathode ray kymograph, and electromyogram The involuntary movements that may be augmented by stimulation are always of the same type as the patient displays spontaneously We have never seen a change to a different involuntary movement other than the characteristic clonic jerks seen with internal capsule stimulation In 2 cases we were unable to elicit these responses, in these instances a temporary mechanical compression in the anatomical area was made by an inflation of the balloon on a Cooper cannula and the patient was tested for the effect

After the surgical target is located by these means the depth electrode is withdrawn, and the ball within the ball and socket device is locked in the correct angle The yttrium 90 bead is delivered in a plastic container from the division of radiotherapy where its activity has been calculated and it has been handled with sterile precautions The bead itself is kept under 3 cm of sterile water during the loading of the carrier loop After loading radiation precautions are observed, and the surgeon quickly transfers the loaded carrier to the stereotaxic device and lowers it to the target A small collar allows the

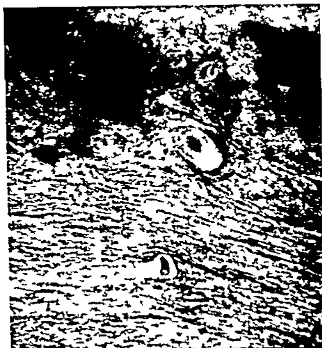


Fig 8 Histologic preparation of rim of a spherical lesion at 14 days showing the coagulation necrosis above next the diapedesis of red cells and the surrounding white matter below H & E stain

carrier rod to be screwed into the top of the ball and another small screw tightens the collar to the rod When its position has been judged to be correct on roentgen films and the apparatus is completely secured the protruding portion of the carrier rod is clipped flush with the collar The scalp is then closed over the entire device Stainless steel sutures over polyethylene tubing are used for a through and through closure and secured by twisting

The bead is left in place for a variable length of time depending on the size of the lesion desired We have usually observed that the alleviation of tremor and rigidity in successful cases gradually proceeds until the total effect is evident on the third day When the yttrium 90 bead is to be removed the procedure is carried out in the ward treatment room With aseptic precautions the wire sutures are loosened the cannula removed and the ball and socket fixation device removed with the tools shown in Fig 3 The bead, kept in fluid in a small glass bottle is returned to the radio therapy department The scalp is reclosed by retwisting the steel wires

There are no problems in postoperative nursing care in regard to radiation safety precautions The head of such a patient has been monitored and the bremsstrahlung, at surface level, has been found to measure less than one and a half times the background level

## Clinical results

This particular group of patients is small in number, and in such a poor risk category as not to be comparable with other series The results are regarded by us as favorable The effects which should be gained in the treatment of Parkinsonism and paralysis agitans are better known than most other dyskinesias In the 9 patients with follow up periods of 4 to 11 months there were 6 who had excellent results This signifies that the patients regained normal motor performance in the affected limbs and relief of rigidity, tremor, and bradykinesia There was one patient who had incomplete relief Two poor results occurred one because of aggravation of a pre existing poor mental status, *and another because of accidental displacement of the yttrium* beads

It is concluded that an excellent result can be obtained by such a technique It is also noteworthy that not one instance of stupor, coma or akinetic mutism occurred in the immediate postoperative course There were no instances of hemiplegia which is usually a complication due to hemorrhage Immediate postoperative side effects, which did occur, consisted of transient confusion, slurred speech, transient hemichorea which usually means partial involvement of the subthalamic nucleus Hypophonia as a late sequel was seen in two patients Hemichorea can perhaps be avoided by 5 mm retraction of the bead when the first sign appears

In order to gain a true evaluation of this kind of operative treatment it will be necessary to carry it out on a large number of patients The present trend, indicated to us in these patients, is however that the lesion can bring about an excellent response, with a freedom from the side effects that often occur as a result of edema and swelling

## SUMMARY

A technique for thalamotomy employing yttrium 90 macrospheres was used in the treatment of Parkinsonism paralysis agitans dystonia musculorum deformans and cerebellar tremors By utilizing the physical characteristics of beta emitters to achieve a circumscribed complete lesion physical disruptive effects are avoided The crucial target the ventrolateral nucleus is subtended by a 1 cm diameter spherical lesion Animal experiments have shown that fixation of the source is necessary to avoid migration of the bead Twelve patients were treated Observation of the patients from 4 to 11 months has shown that an excellent result can be achieved with few or no side effects

## ZUSAMMENFASSUNG

Eine Technik der Thalamotomie mit Yttrium 90 wurde bei der Behandlung von Parkinsonismus paralysis agitans dystonia musculorum deformans und cerebellarem Tremor angewendet Bei Auswertung der physikalischen Charakteristica von Betastrahlern beim Erzeugen von umschriebenen Gewebszerstorungen konnten storende physikalische Nebeneffekte vermieden werden Eine Gewebslasion von 1 cm Durchmesser deckt das zu bestrahlende Gebiet den ventrolateralen nucleus Tierexperimente haben gezeigt dass die Fixierung der Strahlenquelle notig ist um Verschiebungen der Perle zu vermeiden Zwölf Patienten wurden behandelt Eine Nachbeobachtung der Patienten uber 4 bis 11 Monate hat gezeigt dass ausgezeichnete Resultate mit nur geringen oder gar keinen Nebenwirkungen erzielt werden konnen

## RÉSUMÉ

Les auteurs ont utilise une technique de thalamotomie au moyen de spheres d yttrium 90 pour le traitement de la maladie de Parkinson et des syndromes parkinsoniens de la dystonie musculaire deformante (spasmes de torsion maladie de Ziehen Oppenheim) et des tremblements cérébelleux On peut éviter des effets physiques excessifs en utilisant les caractéristiques physiques des emetteurs béta pour obtenir une lésion complete circonscrite La cible qu il importe d atteindre le noyau ventral latéral est contenue dans une lésion sphérique d un cm de diametre L expérimentation animale a montré qu il est nécessaire de fixer la source de radiation pour éviter la migration de la perle Douze malades ont éte ainsi traités et suivis pendant une periode de 4 a 11 mois On a constaté qu on peut obtenir un excellent résultat avec des effets secondaires minimes ou nuls

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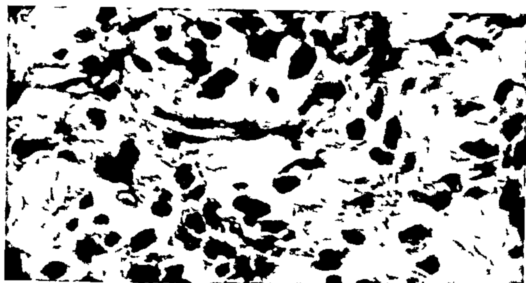
# HEMANGIOBLASTOMA CEREBELLI — REPORT OF A SIX YEAR SURVIVAL AFTER ROENTGEN THERAPY BY TUMOR OSCILLATION THROUGH A GRID

by

HIRSCH MARKS

The incidence of blood vessel tumors comprised only 2 per cent of the total of CUSHING s 2 033 verified intracranial tumors Although not exclusively characteristic of the brain these tumors are relatively important in neuro pathology They may be divided into congenital anomalies and true neoplasms Congenital anomalies usually occur as either venous or arterial malformations These malformations give rise to symptoms resembling those of a brain tumor The reason for these symptoms is usually the size and increased vascularity of the congenital anomalies The venous malformations consist of thin walled large venous vessels the arterial *ones of tortuous arteries Degenerated* brain tissue is often found between the vessels Sometimes recognition of parallel streaks of calcification within the walls of such anomalous vessels, in the conventional skull films is of help to the clinician

Hemangioblastomas are tumors usually of middle life They typify the true neoplasms originating from blood vessels and occur, most commonly within the cerebellum These tumors are brownish in color on their cut surface and show microscopically lacunae with richly cellular tissue in between The cells



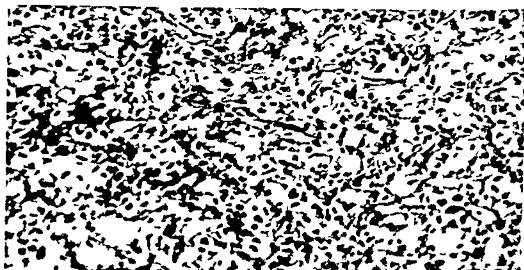


Fig 1 Fat globules suggestive of xanthoma cells may be observed in hemangioblastoma when fat stains are applied

have large oval nuclei with evenly distributed chromatin Fat globules suggestive of xanthoma cells may be observed when fat stains are applied (Fig 1)

Hemangioblastomas are most commonly seen as single lesions They are occasionally associated with angiomatous malformations of the retinae (Von Hippel s disease) or cyst of liver, kidney, ovaries pancreas, etc The combinations of hemangioblastoma of the cerebellum with one or more anomalies in one patient, often familial in nature is known as Lindau s disease (DAVIDOFF & EPSTEIN)

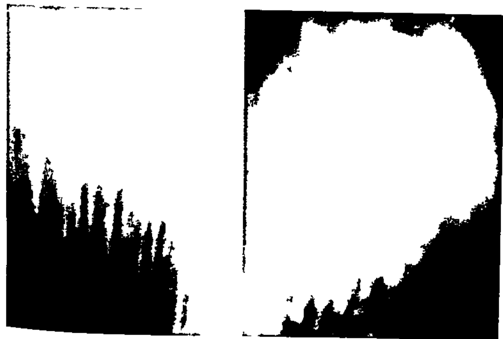


Fig ? Absorption patterns in pendulum grid therap

*Case report* Female, age 36 years Two years before admission she first became aware o pain in th right side of her head which grew progressively in intensity and extent spreading to the eyes and face Recently the headaches were accompanied by vertigo nausea vomiting independent of food intake and on one occasion terminated in loss of consciousness and convulsions The past history revealed hysterectomy at the age of 20 years for excessive bleeding and asthma at the age of 16 years

On neurological examination the patient was seen swaying with eyes open considerable tremor of head ataxic gait with falling to the right side and tremor of the right hand on voluntary movement enunciation with irregular force and rapidity Ophthalmoscopic examination revealed blurred vision nystagmus and bilateral papilledema retinal veins were dilated and tortuous the arteries were constricted and all vessels were broken off at the margins of the disks Spinal fluid studies elicited the following pressure 380 mm of water glucose 80 mg/100 ml chlorides 720 mg 100 ml protein 52 mg/100 ml

Ventriculography showed marked symmetrical dilatation of both l t ral ventricles as well as of the third ventricle with no evident displacement

Operative findings (Schenkman) A reddish blue mass was seen separating the cerebellar hemispheres it was hard to determine whether this mass wa entirely within the fourth ventricle or was arising fror the edge of the right cerebellar hem h re Extreme vascularity prevented the resection of th mass Several small biopsy specim were obtained from this tissue Th gross descripti of the pathologic report (Dolgopol specimen consisted of 4 small fragments of spong grayish white tissue gross section aled some grayish brown areas The microscopic d  osis was Malignant hemangiobl  na



Fig 3 Case of hemangioblastoma of cerebellum No epilation after 4 000 r in air by rotation through a grid 10 × 15 cm absence of any depilatory reaction of the scalp

## Treatment

Roentgen therapy with the use of a grid was instituted by tumor oscillation in an angle of 180 through the sub occipital region The radiation was of quality 1 6 mm Cu HVL, 50 cm STD, 250 kV, grid size 10 × 15 cm with apertures of 0 5 cm in diameter and of an area ratio of 40 % translucent and 60 % opaque The daily dose was 200 r in air The total dose, assessed by the gradual disappearance of the clinical symptoms was reached at 4 000 r in air, and was administered in 20 treatment days, in an overall period of 4 weeks and 4 days

The constant presence and vigilance of the attending radiotherapist are the condition sine qua non of the clinical method of treatment With the symptoms, and not an a priori dose, as the guideposts, one is compelled to discontinue the treatment once the symptoms have attained their vanishing point Some slight symptoms may persist for a while after completion of the treatments However, when they continue unabated, as was the case with our patients, additional treatment must be administered The latter, 1 400 r in air, was delivered with the same factors as above in daily doses of 200 r in air, in an overall *period of 12 days Citrus bioflavanoid compound with ascorbic acid*, 1 500 mg daily, was administered as adjuvant therapy

## Comments

The skin reaction to roentgen irradiation through a grid in rotation is reduced to a minimum and is lowest in anatomical sites approximating a cylindrical configuration

This observation was gleaned from clinical experience about 9 years ago (MARKS 1953, 1954, 1955), at a first attempt at irradiation, by tumor oscillation through a grid, of a patient in extremis This patient had been previously

treated to skin tolerance and returned to work One year later an emergency tracheotomy was performed for a diffusely growing and rapidly expanding carcinoma of the laryngo pharynx with circular metastases to the neck The ensuing total lysis of the malignant process with no concomitant skin reaction except erythema served as a powerful incentive to spur the author on the apply irradiation by tumor oscillation through a grid as the method of choice in all patients for whom encompassing the growth daily was an imperative

This method effectively impedes spread of the growth without the dreaded stress of local and generalized systemic reaction That these reactions were obviated was largely due to the recovery factors inherent in the unirradiated spaces as well as to the higher ratio of tumor to integral dose absorption af forded by this method

The higher ratio of absorption is brought to fruition in the following manner the primary energy impulses emanating from row upon row of grid apertures — upon leaving, on the surface film of the masonite phantom the imprint of a grill (Fig 2), and on the succeeding films beneath it a latticework imprint (Fig 2) — *continue to pursue their paths in the form of a ripple (Fig 2) around* the oscillating tumor in the depth The primary energies along with their secondaries are, therefore diverted away from the periphery toward the re volving tumor center, and the normal tissues outside the irradiated field are consequently relieved of the stress of secondary radiation

Thus a physical therapeutic agent roentgen rays — bedevilled by many side effects of a local and general character which render it impossible of appli cation in tumors of large volume — was converted by oscillation through a grid to a therapeutic agent par excellence, akin in its effectiveness to the or gan affinity or tropism of a chemical agent

**Acknowledgements**

I acknowledge with appreciation and gratitude the kind assistance of Miss Shirley Johnson radiation and isotope technician Miss Victoria Hirschfeld secretary Miss Volda Whittaker and Miss Maria Burton radiation technician

## SUMMARY

A case of unresectable hemangioblastoma of the cerebellum was treated by oscillation through a grid with 250 electronkilovolts The patient has been symptom free for the past 6 years *There was increased selective localization of the radiation energy in the tumor proper and very little in the skin of the scalp*

## ZUSAMMENFASSUNG

Ein Fall mit einem nicht resezierbarem Hamangioblastom des Kleinhirns wurde mit 250 Kiloelektronvolt mittels Oscillation under Verwendung von einem Raster behandelt Der Patient ist seit 6 Jahren symptomfrei Durch diese Technik wurde eine erhohte selektive Lokalisierung der Bestrahlungsenergie im eigentlichen Tumor erhalten weil die Hautbe strahlung *nur gering war*

## RÉSUMÉ

Un cas d hemangioblastome inextirpable du cervelet a été traité par roentgenthérapie pendulaire avec grille sous 250 kV Le malade a survécu sans symptomes ces six dernieres années La localisation sélective de la dose d irradiation a été tres augmentée au niveau de la tumeur et tres faible sur le cuir chevelu

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# IONIZING RADIATIONS AND THE MAMMALIAN EMBRYO

by

ROBERTS RUGH

When considering the biologic effects of ionizing radiations one must never confuse the embryo with the adult into which that embryo develops (RUGH 1962) The reactions of the two are totally different both in degree and in quality Every stage of embryonic or fetal development is more radiosensitive than is the post natal organism by any test applied Lethality is greatest in the early stages just after fertilization, but congenital anomalies occur more frequently following roentgen irradiation at a later stage (Rugh 1959 1961, 1962 RUGH & GRUPP 1959) Still later just before birth neither lethality nor congenital effects are seen but the fetus responds by developing functional sequelae which may not be fully manifest for some years Also it must be remembered after about 5 months for the human the gonads develop and contain primitive germ cells which are themselves very radiosensitive and these cells not only accumulate the damaging effects of radiations in terms of genic mutations but pass them along unaltered to their progeny

When we realize that the embryo and fetus are so radiosensitive we tend to forget that in ionizing radiations we are dealing with a physical entity

Based on work performed under Contract AT (30 1) 2740 for the U S Atomic Energy Commission and aided in part by Public Health Grant B 2116 and RH 97(C2)



Fig 1 a) Mouse egg at moment of invasion by spermatozoon in the process of fertilization Roentgen irradiation at this time is essentially like that of exposure of both gametes separately This stage is very susceptible to roentgen irradiation effects usually resulting in death b) Effect of roentgen irradiation on zygote shortly before approximation of male and female pronuclei Hyperchromaticity of male pronucleus has resulted from 15 r exposure



Fig 2 Upper oviduct of mouse showing four recently fertilized eggs shortly after mating

that is most powerful An exposure which ionizes 1 molecule in 10 million (1 000 r) will kill most adult mammals, and an exposure which ionizes only 1 molecule in 1 000 million molecules (10 r) will cause lymphopenia in the adult and chromosome aberrations and congenital anomalies in the embryo Thus, in contrast with the adult, the embryo and fetus are much more radiosensitive with respect to ionizing radiations which are extremely potent

It has been known for some time that roentgen irradiation of the mammalian embryo at the beginning of neurogenesis will cause the highest percentage of gross CNS anomalies (HICKS et coll 1952, 1953 1954, 1959) This period is about 7 5 to 9 5 days for the rodent (mouse or rat) and about *18 to 25 days* for the human It is likely that any trauma would have a maximum effect in producing these anomalies at such a time, but ionizing radiations are so penetrating so instantaneous in their impact that as many as 48 % of the




Fig 3 a) Fragmentation of fertilized egg by 15 r exposure at the stage seen in fig 2 Pieces of cytoplasm are pinched off but both pronuclei remain in the larger fragment of cytoplasm b) Complete fragmentation of zygote from 15 r exposure c) Exposed zygote pinching off cytoplasm but this time the pronuclei are contained within the discarded material The remaining cytoplasmic mass without either nuclear component could not survive While 15 r can cause these effects their occurrence is statistically low

mouse embryos exposed at 8 5 days will develop the severe cerebral anomaly known as exencephaly or brain hernia (RUGH & GRUPP 1959 1961, 1962)

Following the completion of organogenesis it is impossible to produce gross congenital anomalies by means of ionizing radiations Some anomalies can indeed, be caused but they affect the cytarchitecture of the brain on an histologic level It is now believed that levels of exposure much lower than the 200 r referred to will elicite functional effects not always manifest at birth In fact there is evidence that behaviour effects evident through electroencephalography and possibly other mental disturbances may follow by years the exposure, even at low levels, of the late fetus

Prior to the onset of neurogenesis at about 7 5 days in the mouse embryo it had long been assumed that congenital sequelae could not be elicited by ionizing radiations (RUSSELL 1950 1956 1957 RUSSELL & RUSSELL 1956) This was because rather high levels of irradiation were used so that most of the early embryos were killed It is the surviving but damaged embryo that shows the congenital anomaly so that a dose which kills off the majority of early embryos would be one to actually reduce the incidence of congenital anomalies

Recently it has been demonstrated that exposures of as little as 10 r to the mouse embryo in the 2 cell stage can cause the development of exencephalia the cerebral hernia True it does not occur in great frequency but the fact that it occurs at all in a strain of mice where it had never before been seen among the controls suggests that possibly even 10 r is not the threshold dose for congenital effects (This anomaly has recently been seen among non irradiated controls the frequency being 3 in 18 000 control embryos )

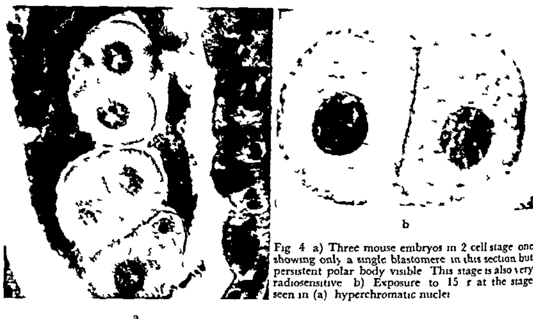


Fig 4 a) Three mouse embryos in 2 cell stage one showing only a single blastomere in this section but persistent polar body visible This stage is also very radiosensitive b) Exposure to 15 r at the stage seen in (a) hyperchromatic nuclei

Exencephalia brain hernia is a developmental defect which prevents the closure of the neural folds at the mid brain level, so that the cranial roof does not form properly and the brain protrudes through the skull roof This and the related anencephaly occur at a rate of about 1 in 500 cases of human births, but can be produced regularly in rodent embryos by roentgen irradiation at certain times Whether background or even extended diagnostic ir radiation might be the cause of this anomaly in human births is, at this time, still conjecture However, it must be suggested that the human embryo is probably substantially like the rodent embryo in regard to radiosensitivity, and while we cannot extrapolate from the rodent to man, we should take rodent data as suggestive

The above statements have been made on the basis of findings with over 60 000 mouse embryos and fetuses, examined shortly before and after birth It so happens that the mouse, producing congenitally abnormal newborn will kill and devour them immediately so that it is necessary, in order to obtain reliable statistical data, to study most of these fetuses just before the time of expected birth

Current studies are directed toward a further understanding of the relation of embryonic or fetal exposure and a large variety of congenital anomalies However it seems quite definite that the studies will have to be directed to the levels of electron microscopy for structural effects and to the electroenceph alogram the electroretinogram, and standard behaviour tests, to determine

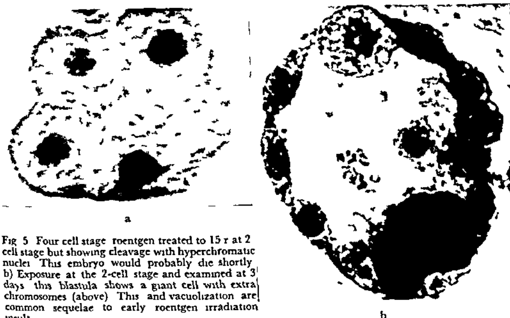
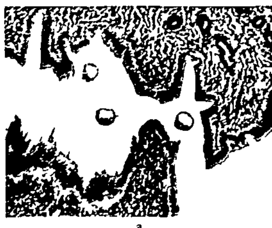


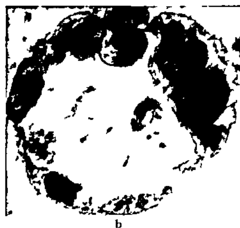

Fig 5 Four cell stage roentgen treated to 15 r at 2 cell stage but showing cleavage with hyperchromatic nuclei This embryo would probably die shortly b) Exposure at the 2-cell stage and examined at 3 days this blastula shows a giant cell with extra chromosomes (above) This and vacuolization are common sequelae to early roentgen irradiation insult

effects not seen by histopathology Further we are forced to lower the exposure level and are currently studying the effect of 1 5 and 10 r single exposure at each and every 24 hour period from fertilization to 18 5 days gestation Em bryos and fetuses thus exposed are being analyzed for immediate effects as well as those long term sequlae such as sterility leukemia, cataracts ageing and the incidence of a variety of tumors

Diagnostic radiology is as essential to medical practice as the scalpel is to the surgeon Ionizing radiations, used for peaceful purposes have and will advance civilization more rapidly than any other single physical aid known to man Therapeutic levels of roentgen irradiation are saving the lives of thou sands by treatments every day Thus there is no justification in condemning ionizing radiations upon the realization that they can be so devastating to the embryo and fetus Rather the clinician should be informed of these findings and urged to protect the gravid uterus in all instances of pelvic irradiation Further since the human embryo is probably most radiosensitive at a time when a pregnancy is least suspected namely between 15—42 days after the onset of menstruation, it is rapidly being an accepted practice to limit exten sive radiodiagnosis of the female pelvis to the first 9 days following the onset of menstruation in order to avoid the earliest stages of an unsuspected preg nancy In this way we may eventually reduce the 5 % incidence of congenital anomalies expected in human births



a



b



c



d



e



f

Fig 6 For legend see opposite page



Fig 7 When mouse embryos are exposed at 3 5 days (Cf fig 6a) to 50 r and surv ve they may develop these severe cephalic anomalies found n the sole survivors of a single litter The damage appears to be largely of the CNS and anterior although ther are always some in ternal anomalies such as of the kidney heart etc Such ind viduals could not survive

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Legend to *Fig 6* *a)* *Three blastula* suspended with n the ute ine lumen at 3 5 days after copulation in the mouse Thes would be expected to implant w thin 24 hours and a h ghly radiosensitive *b)* *Blastula* exposed to roentgen rays sho ing vacuolizat on of some cells (above) c) Roentgen irradiation at the blastula stage (shown in a) but allowed to develop to time of implantation (shown in d) and accumulation w thin the blastocoel of loose cells wh ch have been discarded by this early embryo If such an embryo should survive and develop it would be deficient to the extent of these disca ded cells propo tionately to the total number *of cells of the blastula* d) Normal implantat on at 4 5 days after copulat on e) Neu al groo e at 7 5 days de elopment when there is abundant neu ectoderm be ng transfo med nto neuroblast wh ch are extremely radiosens tive If exposed to roentgen rays in excess of 25 and examined with n 24 hours t can be seen that many of the sensitive cells have been killed (se next view) f) Neural groo e 24 hours after roentgen irradiat on showing many pyknotic cells and many being sloughed off nto the exterior of the embryo Survival would result in a neural defic nt embryo and fetu

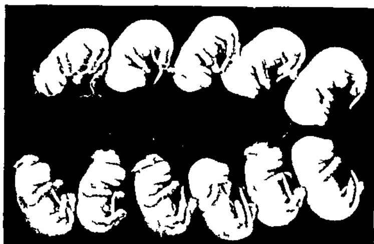


Fig. 8. An entire litter as found in the bicornuate uterus of the mouse at 18.5 days showing 5 out of 11 members with the extreme cerebral anomaly known as exencephalia or brain hernia. This was due to exposure to 200 r at 8.5 days of development when the neuroblasts of the CNS were most abundant.



Fig. 9. Heterozygosity is a protective variable for adult mice known as heterosis but this does not apply to the embryo. This is a litter of hybrid mice (CF1 × C57) exposed at 8.5 days to 200 r showing a variety of anomalies from minor stunting (upper left) to death and resorption (lower right). Intermediate effects are exencephaly and gross stunting.



Fig 10 One instance of hereditary exencephalia caused by exposing the female mouse to 100 r and breeding her to a normal male This anomaly appeared in three successive generations though infrequently therefore genetic



Fig 11 Enlarged view of exencephalia brain hernia due to interruption of development of the brain and the covering cranial roof The balance of the head including the eye appears to be rather normal

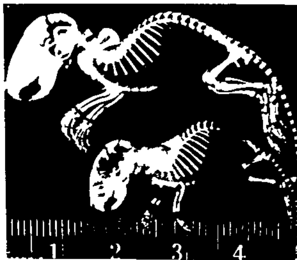



Fig 12 Roentgen views of the skeleton at birth of a normal (above) and a fetally roentgen irradiated (below) mouse skeleton showing that there is topographical normality though extreme stunting in the exposed mouse This is due to cell loss at an early stage the remaining cells being utilized by the embryo as a whole to develop a well balanced though reduced individual

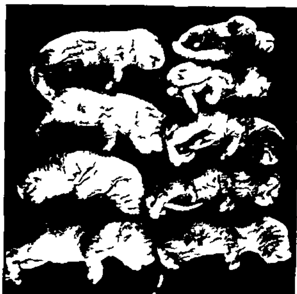


Fig 13 An entire litter of rats at birth following exposure to 100 r at 9 5 days embryonic development The great variety of anomalies occurring within the single litter exposed to identical roentgen irradiation is notable



Fig 14 Enlarged view of few members of litter seen in fig 13 to show gross anomalies largely involving the central nervous system



Fig 15 Entire l tter of rat embryos just before time for del very show ng death and resorption of three dead fetuses also three in number and the remaining fetuses reduced but still to look more like mouse em bryos



F g 16 Hemi sected skulls of two rats at 2 weeks of age ho ing (abo e) control with normal brain and (below) roentgen irrad ated to 100 r in ut ro at 9 5 days showing collap ed bra n of hydrocephalus ind vidual



*Fig 17 Gross sections (transverse) of brains of rats at 2 months of age The single control to the left and other five are members of a single litter showing various degrees of hydrocephalus*



Fig 18 Control to the left and two brains of hydrocephalic rats treated by 100 r at 9 5 days gestation These roentgen irradiated brains are also grossly distorted

## SUMMARY

It has been found that the mammalian embryo shows varying reactions to ionizing radiations such that it is always more radiosensitive than is the adult into which it develops at some stages 100 times as sensitive After neurogenesis is completed congenital anomalies of that system are rarely produced but exencephaly (*brain hernia*) has been caused by ionizing radiations impinging upon the 2 cell stage of the mouse with an exposure of as little as 10 r

## ZUSAMMENFASSUNG

Es wurde gefunden dass der Saugetierembryo gegenuber jonisierter Strahlung verschieden artige Reaktionen zeigt So ist er ca 100 mal strahlenempfindlicher als das erwachsene Mutter tier das den Embryo in sich tragt Nach vollzogener Neurogenesis sind congenitalen Missbildungen des Nervensystems selten Jedoch konnte mit so einer geringen Dosis jonisierter Strahlung wie 10 r im 2 Zellstadium bei der Maus Excenphalie (zerebrale Hernienbildung) verursacht werden

## RESUMÉ

On a constaté que les embryons de mammiferes ont des réactions variables aux radiations ionisantes et sont toujours plus radiosensibles que l adulte dans lequel ils se développent a certains stades 100 fois plus sensibles Quand la neurogénèse est terminée les anomalies du systeme nerveux surviennent rarement mais l exencephalie (hernie cérebrale) a été provoquee par des radiations ionisantes au stade de 2 cellules chez la souris avec des doses ne dépassant pas 10 r

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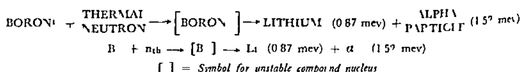
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# BORON-SLOW NEUTRON CAPTURE THERAPY OF GLIOMAS

by

W H Sweet A H Soloway and G L Brownell

The type of radiation following capture of slow neutrons presents a possible method for destroying tumor rootlets which remain after surgical extirpation of cerebral neoplasms



BORON + THERMAL NEUTRON → [BORON ] → LITHIUM (0 87 mev) + ALPHA PARTICLE (1 57 mev)

$B + n_{th} \longrightarrow [B] \longrightarrow Li$ (0 87 mev) $+ \alpha$ (1 57 mev)

[ ] = *Symbol for unstable compound nucleus*

When the isotope boron 10 captures a slow neutron the ensuing compound nucleus disintegrates at once into a lithium atom and an alpha particle These share between them the huge energy, 2 4 million electron volts which is also evolved But because of the relatively enormous size of the particles they travel only about 8 microns in tissue Hence the destruction they cause is confined to the site of the disintegrating atom The greater the concentration of boron 10 in tumor than in brain the greater the differential injury to the tumor

During the last 8 years 140 boron compounds have been studied by Soloway (1, 2, 4, 5 6) in mice, bearing gliomas re the differential tendency of the compounds to enter the tumors and in larger animals as well for their toxicity

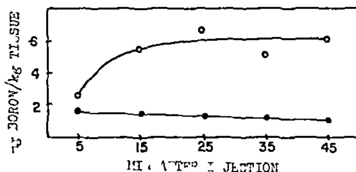



Fig 1 Boron concentration in man intravenous injection of 3 mg/kg p-carboxyphenylboronic acid The curve marked with empty circles represents 17 biopsies in 7 patients with glioblastoma The curve marked with filled circles represents 15 biopsies in 6 patients with normal brain

The 6 most favorable of these have then been given intravenously in small doses to patients while they were undergoing craniotomy for tumor The tumor and any normal brain necessarily removed with it were assayed for boron Fig 1 is a plot of boron concentration against time for glioblastoma and for normal brain in man when the compound given was paracarboxybenzene boronic acid The tumor to brain ratio 15 to 45 minutes after injection rises slowly from 3 to 1 up to 5 to 1

De Rougemont and Soloway have demonstrated that the barrier mechanism between blood and normal brain in the dog recovers from the insult of cerebral lobectomy within three weeks

Hence we seek in our patients to carry out the irradiation from the boron slow neutron capture 2 to 3 weeks after the grossly total resection of the tumor The original wound is completely re opened in a special operating theatre (Fig 2) beneath the core of the nuclear reactor of the Massachusetts Institute of Technology Scalp muscle and bone which like tumor take up much boron are widely reflected in order to minimize radiation injury to them (Figs 3 and 4) We place thin gold foils on cerebral surfaces and tiny gold wires into the depths of the brain

Following the irradiation we measure from the radioactivity induced in the gold the slow neutron dose From these analyses and those for boron uptake obtained at the first operation on each patient we arrive at a first approximation of the dose due to heavy particles Moreover since the slow neutrons penetrate matter poorly we also remove the cerebrospinal fluid at the lobectomy site and if necessary replace it by an air filled balloon A tube to the bottom of the field is connected to suction for preventing accumulation of cerebrospinal fluid during the 30 to 105 minute period of irradiation The patient is elevated to the ceiling portal we leave the room but give anesthesia and check the vital signs from the adjoining area outside the concrete shield

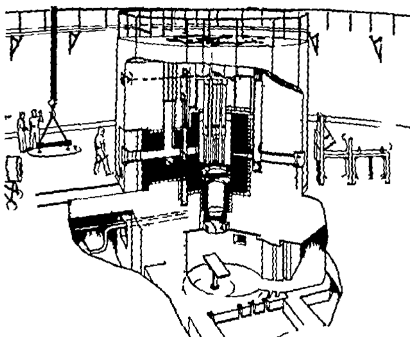


Fig 2 Cut away diagram of M I T nuclear reactor The operating room lies directly below the core of the reactor A hydraulic lift on the operating table permits elevation of the patient to the ceiling when the wound has been reopened Shutters above the ceiling portal in the operating room are independently controllable so that all other reactor studies proceed without interference

Between mid November 1960 and mid August 1961 we irradiated 16 patients after intravenous injection of paracarboxybenzeneboronic acid made with boron 10 Eight of these have already died from 2 to 6 months after irradiation and the post mortem material from 7 of them is still under study Tentatively however we can say that our tactic has not given enough radiation to tumor cells The dose to neoplasm at the surface of cut face of brain has been steadily increased from 4 000 to 16 000 rad Normal brain received about 1/3 that amount Among the 12 patients irradiated between 4 and 10 months ago there is but one excellent result That we did achieve some destruction of tumor is suggested by a comparison between the next two pairs of figures The radio arsenic scan of a patient with a glioblastoma just before operation and the typical residual tumor seen 43 days after a grossly total removal via lobectomy, are seen in Fig 5 In Fig 6 are shown the scans of another patient just before operation and 56 days after similar surgery plus reactor radiation 34 days previously Although almost no tumor can be seen here, it did recur and has since killed the patient

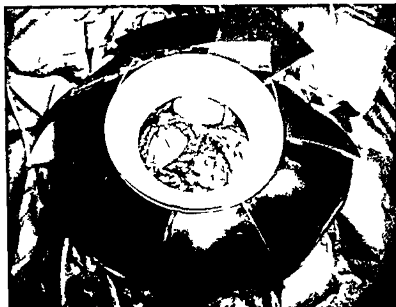
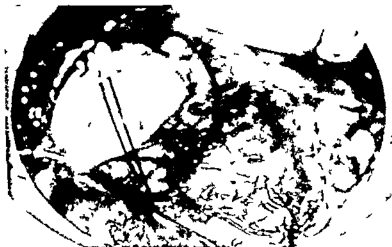


Fig 3 General vie of the right frontal lobe prepared for radiation A w hite circular boron loaded ceramic cone surrounds the area of exposed brain The anterior frontal zone of previous tumor removal is filled w th an air inflated balloon (at 8 to 10 o clock near periphery of inner circle enclosed by cone) This facil tates access of the slow neutrons to the cerebral area containing tumor remnants Another lith um filled rubber balloon — 11 to 1 o clock at periphery of inner c rcle — protects underlying tempo al muscle from neutron radiation The black flaps hanging down from the outer circumference of the wh te cone are a boron loaded plastic to protect the remainder of the head and neck f om this radiation



F g 4 Clos up view of s te prepared fo adiat on The a r fill d balloon in the area of pre ous p t al lobectomy is anchored in place by a silk sutu e through the dura flected m dially at th upe rior m dline

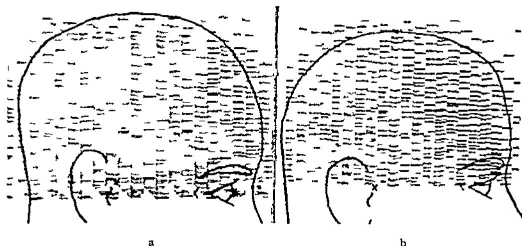


Fig 5 *Positrocephalograms in one and same patient* a) *Pre operatively* of a radioarsenic scan *showing* dense concentration in a posterior inferior frontal glioblastoma b) 43 days after grossly total removal of the glioblastoma Abnormal isotopic uptake in the original area is still recognizable

In our next series which has already started with one patient we are giving sodium perhydrodecaborate $Na_2B_{10}H_{10}$ Advantages over our previous compound are (1) this molecule has a far greater percentage of boron (2) *it is* less toxic and we have given it in doses up to 50 *mg* of boron per kg of body

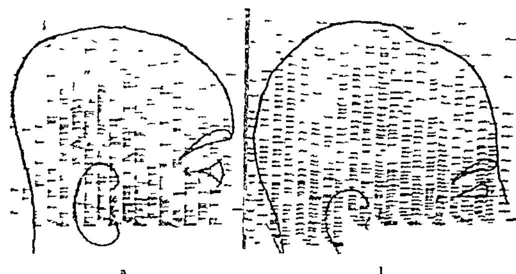
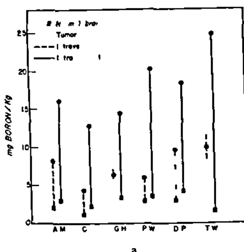
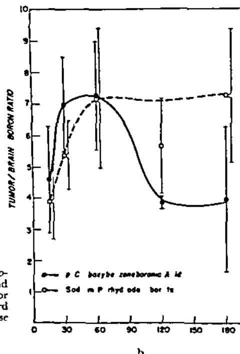


Fig 6 Positrocephalograms in one and same patient a) Pre-operatively of a radioarsenic scan showing dense concentration in a temporo parietal glioblastoma *b)* ?6 *days after grossly total removal* of tumor and 34 days after boron slow neutron reactor therapy More striking reduction in abnormal isotopic uptake than in the non irradiated patient in fig 5




a




b

Fig 7 a) *Glioblastoma multiforme sodium perhydrodecaborate* Comparison between intravenous and intra arterial injections of uptake in brain and tumor in human subjects b) Mice studies with standard deviations *Uptake of two boron compounds by mouse* brain and mouse gliomas

weight without ill effect (3) it maintains a high tumor to brain ratio of nearly 7 to 1 in mouse gliomas longer than the paracarboxy compound (Fig 7a) and (4) it is water soluble at pH 7 4 and can be injected directly into the common carotid artery distal to temporary occlusion of that vessel and with the external carotid tied off (Fig 7b) In the 6 patients illustrated here a portion of tumor and contiguous normal brain was removed following intravenous injection of 3 mg per kg of $Na_2 B_{10}H_{10}$ Then about 1 hour later the same amount was injected directly into the proximally occluded ipsilateral common carotid artery and the extirpation of the tumor was concluded We find an average of about 2 1/2 times as much boron in tumor after the second injection contrasting with 1 1/2 times as much in normal brain thereafter We have exploited this tactic still further by irradiating our first patient after an injection of $Na_2 B_{10}H_{10}$ while both common carotid arteries were occluded Another favorable change in our physical facility has occurred namely a doubled output of the reactor from 1 to 2 megawatts permitting a lowering of the unwanted gamma dose from the reactor core

Aided by these two major changes we hope our next series of patients will show more satisfactory responses than the first group

## Acknowledgements

We are grateful to the supporters of this research U S Atomic Energy Commission under contract No At (30—1)—1093 National Cancer Institute U S Public Health Service Grant No C-3174 Rad and a grant by the John A Hartford Foundation on Isotopic Radiation Therapy of Neoplasms

## SUMMARY

The most favorable among 140 boron compounds studied in mice bearing gliomas have been checked for their toxity in larger animals and of these the six best have been finally assayed in man for use in neutron capture therapy by analyses of tissue uptake during craniotomy and by toxicity and excretion studies in terminal glioma patients An initial series of 16 patients were irradiated using intravenous injection of paracarboxybenzene boronic acid made with boron 10 Dosimetric and operative techniques are described Treatment of a second series has begun using an even less toxic compound containing far more boron and suitable for intracarotid injection following temporary occlusion of both the common carotid arteries

## ZUSAMMENFASSUNG

Die aussichtsreichsten der 140 Bor Verbindungen die an Mausen mit Glioma studiert wurden wurden an grosseren Tieren bzgl ihrer toxischen Wirkung untersucht Die 6 besten Verbindungen wurden schliesslich am Menschen zwecks Neutronenbestrahlung ausprobiert, wobei die Aufnahme ins Gewebe wahrend einer Kraniotomie die Toxizitat und die Ausscheidungsverhaltnisse bei Patienten mit terminalen Gliomen studiert wurden Zu Beginn wurde eine Gruppe von 16 Patienten unter Anwendung von paracarboxybenzen Borsaure aus Bor 10 hergestellt behandelt Die dosimetrische und operative Technik wird beschrieben Es wurde eine Behandlungsserie begonnen wobei eine geringer toxische Verbindung zur Anwendung kam *Sie enthalt bedeutend mehr Bor und eignet sich fur Injektion* in die Arteria carotis im Anschluss an temporaren Verschluss beider AA carotis commun

## RÉSUMÉ

Parmi 140 composés du bore expérimentés sur des souris porteuses de gliomes les plus favorables ont été testes au point de vue de leur toxicité sur des animaux plus gros Les six meilleurs de ces composés ont été essayés sur l homme en vue de leur utilisation pour un traitement par capture de neutrons cette expérimentation faite sur des malades atteints de gliomes au stade terminal a comporté des analyses de fixation tissulaire au cours de craniotomies et des études de toxicité et d excrétion Une premiere série de 16 malades a été irradiée après injection intraveineuse d acide paracarboxybenzène borique fait avec du bore 10 Les auteurs décrivent la technique du traitement et de la dosimétrie Le traitement d une seconde série a été entrepris avec un composé encore moins toxique contenant beaucoup plus de bore et utilisable en injection intracarotidienne apres occlusion temporaire des deux carotides primitives

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AUS DER NEURORADIOLOGISCHEN ABTEILUNG DES STRAHLENINSTITUTS (DIREKTOR PROF DR H OESER) DER FREIEN UNIVERSITÄT BERLIN, DEUTSCHLAND

# NACHWEIS VON CEREBRALEN STRAHLENSCHÄDEN MIT RADIOAKTIVEN SUBSTANZEN

von

SIGURD WENDE

Um den Einfluss einer Röntgen Tiefentherapie auf die Blut Hirn Schranke festzustellen, erfolgte bei Patienten, die wegen eines bösartigen Hirntumors bestrahlt wurden zu wiederholten Malen eine Gamma Encephalographie Die technische Durchführung dieser Gamma Encephalographie wurde bereits in , Ergebnisse der Hirntumor Diagnostik mit radioaktiven Substanzen geschildert

Wir führten weiterhin tierexperimentelle Untersuchungen durch um das erste Auftreten einer bestrahlungs bedingten Permeabilitäts Störung der Blut Hirn Schranke erfassen zu können

Die Abb 1 zeigt die Differenz Prozent Kurven einer Patientin mit einem Astrocytom rechts fronto parietal Die beiden oberen Kurven geben die 2 Std Werte vor und nach Beginn der Röntgen Therapie und gleichzeitiger RISA Injektion an Es ist dabei deutlich zu erkennen, dass nach der 1 Röntgen Bestrahlung von 150 r auf die rechte Parietal Region eine erhebliche Impuls Zunahme gegenüber der 1 Messung bei der Voruntersuchung zu verzeichnen ist 24 Std später wurde die linke Parietal Region ebenfalls mit 150 r bestrahlt Die anschliessende Gamma Encephalographie zeigte ein unregelmässiges Kurvenbild Zwar besteht noch immer ein Impuls Überwiegen der Tumor Seite also auf der rechten Hemisphäre, über dem Bestrahlungsfeld bei Pr, ist es nun jedoch zu einer deutlichen Impuls Erhöhung gekommen

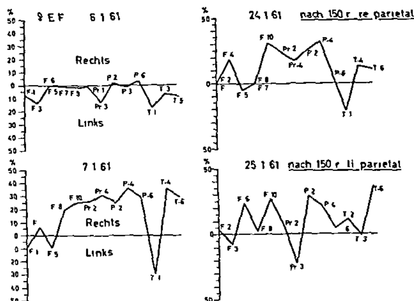



Abb 1 Differenz Prozent Kurven eines Astrocytoms vor und bei Rontgen Therapie

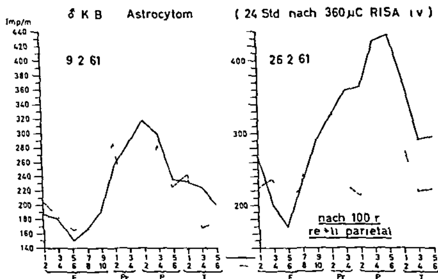



Abb 2 Impuls-Kurven eines Astrocytoms vor und bei Rontgen Therapie

Ein ahnliches Ergebnis zeigt die Abb 2 Es handelt sich dabei um einen Kranken mit einem Astrocytom links parietal Auf der linken Seite des Bildes finden sich die Impuls Kurven 24 Std nach RISA Injektion Die Impuls Erhohung uber dem Tumor Gebiet ist deutlich erkennbar Die Kurven auf

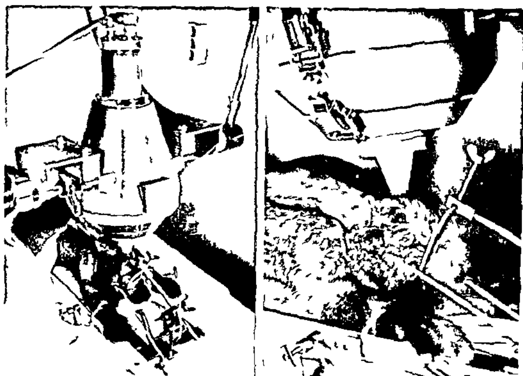


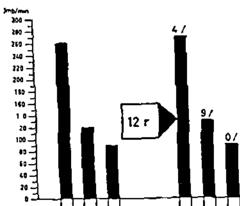
Abb 3 und 4 Tier Versuchsanordnung fur die Isotopen Diagnostik

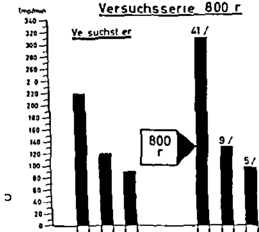
der rechten Seite des Bildes geben wiederum die Impuls Werte 24 Std nach RISA Injektion wieder Diesmal erfolgte aber vorher eine Rontgen Bestrahlung des Gehirns mit 100 r rechts und links parietal Durch diese Rontgen Therapie hat die Impuls Hohe uber allen Hirnabschnitten deutlich zugenommen

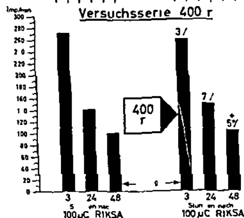
Die signifikante Impuls Erhohung sofort nach Beginn der Bestrahlung lasst sich auf eine Permeabilitats Storung der Blut Hirn Schranke zuruckführen Diese Permeabilitats Storung macht sich im klinischen Bild mit einer Zunahme des Hirndrucks bemerkbar es tritt eine deutliche psychische Verlangsamung bis zur Somnolenz ein Derartige Veranderungen konnen als Zeichen eines zunehmenden Hirnodems aufgefasst werden das sich durch die Gamma Encephalographie objektivieren lasst

Um Beginn und Ablauf des cerebralen Strahlenschadens bzw des Hirnodems erfassen zu konnen, erfolgten tierexperimentelle Untersuchungen nach umschriebener Rontgen Bestrahlung des Gehirns

Die Impuls Messungen uber der Schadelkalotte wurden in gleicher technischer Anordnung durchgeführt, wie sie bereits bei der Patienten Untersuchung geschildert wurde Als Versuchstiere wurden ausgewachsene Kaninchen



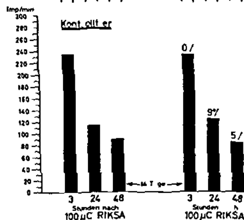




Abb 5 Impuls Werte vor und nach Bestrahlung von 12 r bzw 400 r

Abb 6 Impuls-Werte vor und nach Bestrahlung von 800 r

mit einem Durchschnittsgewicht von 2 5—3 kg verwandt Die Tiere erhielten vor jeder Untersuchung zur Blockierung der Schilddruse eine intravenose Jod Injektion dann wurden 100 $\mu$C radioaktives jodiertes Kaninchen Serum Albumin (RIKSA) injiziert Die Impuls Messungen erfolgten 3 Std 24 Std und 48 Std spater Bei der Untersuchung waren die Kaninchen auf einem Tierbrett fixiert dadurch wurden Bewegungen des Kopfes mit den daraus resultierenden Messungenauigkeiten unmoglich Die Messungen erfolgten bei freigelegter Schadelkalotte sowohl uber der Area agranularis praecentralis als auch uber der Area striata (Abb 3 und 4)

Nach einer Voruntersuchung zur Bestimmung des Ausgangswertes fanden dann im Abstand von 14 Tagen die weiteren Untersuchungen statt Vor der 2 Isotopen Injektion erhielten die Tiere eine einmalige umschriebene Ront

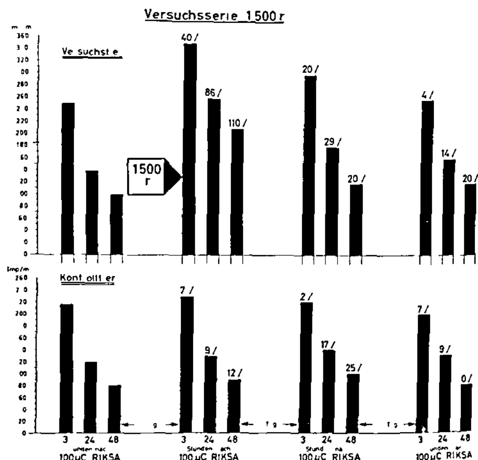



Abb 7 Impuls-Werte vor und nach Bestrahlung von 1 500 r

gen Bestrahlung des Gehirns Die verabfolgte Dosis betrug je Versuchstier 12 r —5 000 r Jeweils 5 Tiere wurden zu einer Versuchsserie zusammengefasst, 3 Tiere wurden bestrahlt 2 Tiere dienten zur Kontrolle Der Abstand von 14 Tagen zwischen den einzelnen Untersuchungen wurde eingehalten, um eine vollstandige Ausscheidung der vorher injizierten radioaktiven Substanz zu gewahrleisten

Die Abb 5 zeigt die Impuls Werte bei den Versuchsserien „12 r" und „400 r" Es ist zu erkennen dass bei der Messung nach der Bestrahlung keine Erhohung der Impulse gegenuber den Werten der Voruntersuchung aufgetreten ist Die Versuchsserien „25 r" „50 r", „100 r" und „200 r" zeigten das gleiche Ergebnis

In der folgenden Abb 6 sind die Werte der Versuchsserie „800 r" wiedergegeben Auf dem oberen Teil der Abbildung sind die Ergebnisse der Voruntersuchung und die Impuls Hohen nach der Rontgen Bestrahlung dargestellt

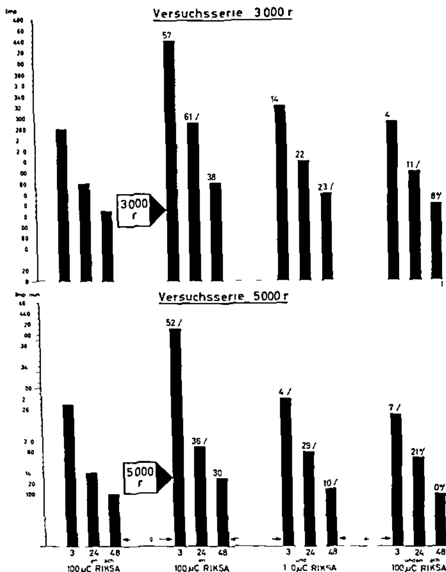



Abb 8 Impuls Werte vor und nach Bestrahlung von 3 000 bzw 5 000 r

Es findet sich hier ein deutlicher Impuls Anstieg 3 Std nach der Bestrahlung während die Werte 24 Std und 48 Std später keine Abweichung gegenüber der Voruntersuchung aufweisen Der untere Teil der Abbildung zeigt die gleichbleibenden Mess Ergebnisse der Kontrolltiere

Noch deutlicher kommen die Veränderungen bei der Versuchsserie ,1 500 r zum Ausdruck Wiederum auf der oberen Hälfte der Abb 7 sind die Impuls

Höhen bei den bestrahlten Tieren angegeben Hier liegt der 3 Std Wert 40 % über dem Mess Ergebnis der Voruntersuchung Die Messungen nach 24 Std bzw nach 48 Std zeigen dass die Zunahme der Impulse pro Minute gegenüber der betreffenden Voruntersuchung sogar 86 % bzw 110 % beträgt Im Gegensatz zur Versuchsserie „800 r ist hier also nicht nur eine Impuls Erhöhung sondern auch ein erheblich verzögerter Abfall der Messwerte fest zustellen Die Untersuchung weitere 14 Tage später ergibt, dass die Impulse gegenüber den Ausgangswerten noch mässig erhöht sind

Vergleicht man dazu die Messungen bei den Kontrolltieren der gleichen *Serie (untere Hälfte des Bildes)* so ist keine sichere *Differenz* zwischen den *einzelnen Untersuchungen* erkennbar

Die Abb 8 zeigt die Versuchsserien „3 000 r und „5 000 r Auch hierbei lässt sich wieder die erhebliche Zunahme der Impuls Höhe nach der Röntgen Bestrahlung erkennen

Aus den tierexperimentellen Untersuchungen kann geschlossen werden, dass nach einer umschriebenen Röntgen Bestrahlung des Gehirns eine Perme abilitäts Störung der Blut Hirn Schranke auftritt Sie stellt sich in ähnlicher Form auch nach der Röntgen Bestrahlung von Patienten mit Hirn Tumoren ein Diese Permeabilitäts Störung kann mit der Gamma Encephalographie *durch die Zunahme der Impulse gegenüber dem Messergebnis der* Vorunter suchung objektiviert werden Sie beginnt sofort nach der Bestrahlung und klingt dann allmählich ab Vier Wochen später ist die Ausgangslage wieder er reicht

Unsere Messergebnisse haben ihre Parallele in den histologischen Unter suchungen, bei denen sofort nach der Röntgen Bestrahlung des Gehirns ein perivasculares Ödem festgestellt werden kann das sich nach einiger Zeit wieder zurückbildet

## ZUSAMMENFASSUNG

*Nach einer umschriebenen Röntgenbestrahlung des Gehirns stellt sich eine* Permeabili täts Störung der Blut Hirn Schranke ein die sich mit der Gamma Encephalographie ob jektivieren lässt

## SUMMARY

Localized roentgen irradiation of the brain causes increased permeability of the blood brain barrier which is demonstrable by means of gamma encephalography

## RÉSUMÉ

L irradiation roentgen localisée du cerveau augmente la perméabilité de la barrière hémo cérébrale que l on peut mettre en évidence grâce à la gamma-encéphalographie

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## FURTHER ATTEMPTS TO INFLUENCE THE ELIMINATION OF RADIOSTRONTIUM

by


ARNE NELSON, CURT RONNBACK and LENA ROSEN


In an earlier investigation the effect of Sr chloride Sr lactate Ca chloride, Ca lactate Na lactate $CaNa_2EDTA$ and $CaNa_2$ citrate on the elimination of radiostrontium after intraperitoneal injection was examined in mice (CARLQVIST & NELSON 1960) Only strontium salts and calcium sodium citrate of the tested agents were able to decrease the retention if given within half an hour before or after the administration of radiostrontium The optimum effect was obtained with Sr chloride the effect of Sr lactate being less All other agents tested increased the retention

In spite of the high number of animals giving statistically significant results we considered that some of them required further confirmation It was therefore decided to repeat some of the investigations using a different method of measurement of the retention of radiostrontium In the previous study $^{89}Sr$ was used and the radioactivity was measured with a G M detector and a conventional scaler after ashing of carcasses (method I) In the present investigation $^{85}Sr$ which is a $\gamma$ emitter was employed and the retention in each animal measured after different intervals by means of a small animal counter with a plastic scintillator (method II)


From the Medical Division Research Institute of National Defence Department 1 Sundbyberg Sweden


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**Table 1**

*Experimental conditions*

| Agents | Concentration | Dose mM/kg | No of animals |
|---|---|---|---|
| Phys saline (controls) | 0 9 % | — | 30 |
| Sr chloride | 0 2 M | 2 0 | 30 |
| Sr lactate | 0.2 M | 1 5 | 30 |
| Sr » | 0 2 M | 2 0 | 29 |
| Ca chloride | 0 2 M | 1 0 | 53 |
| Ca lactate | 0 2 M | 1 0 | 30 |
| Ca « | 0.2 M | 1 5 | 28 |
| Na » | 0 2 M | 1 0 | 29 |
| Na » | 0 2 M | 2 0 | 28 |
| Na rhodizonate | saturated | about 0 3 | 30 |
| Mg sulfate | 0 2 M | 3 0 | 30 |
| CaNa EDTA | 0 2 M | 2 0 | 30 |
| CaNa EDTA | 0 4 M | 4 0 | 30 |
| CaNa DTPA | 0.2 M | 2 0 | 60 |
| CaNa DTPA | 0 5 M | 5 0 | 20 |

## Materials and Methods

*Mice* CBA mice males all aged 75 to 80 days, were used in the study, total number of animals 460 divided into groups of 8 to 10 as seen in Table 5

*Radiostrontium* Carrier free strontium 85 in nitric acid was neutralized and diluted with physiologic saline Each animal was given a volume of 0 5 ml containing about 0 1 $\mu$C $^{85}$Sr Due to the decay of the radionuclide the concentration of the radiostrontium solution had to be corrected in order to produce the same radioactive dose in the same amount of solution, i e 0 5 ml The injections of radiostrontium were made intraperitoneally (i p )

*Agents* The different agents (see Table 1) were also administered i p to the animals 30 and 10 min before, and 10, 30 and 60 min and 24 hrs after the administration of radiostrontium The controls received 0 5 ml normal saline at the time intervals given above The doses of the various agents are expressed as millimoles per kilogram bodyweight (mM/kg)

*Measurements* The measurements have been performed with a 'small animal counter, built at our institute (NILSSON 1961) The detector is a large well shaped plastic crystal the dimensions of the well are length 210 mm and diameter 90 mm A photomultiplier tube with a relatively large cathode diameter, 110 mm, is attached to the scintillator The effectiveness of the detector is about 30 % A discrimination to give the best value of the ratio counts of sample/counts of background under the given circumstances was made (RÖNNBÄCK 1962)

**Table 2**

*Retention in controls at different times after injection of $^{85}Sr$ as percentage of initial measurement (per centage of dose administered)*

| | Not corrected for decay | Corrected for decay |
|---|---|---|
| 1 day | 65.1 | 65.8 |
| 3 days | 51.9 | 54.0 |
| 7 days | 43.9 | 47.9 |
| 10 days | 39.6 | 43.7 |
| 14 days | 37.3 | 41.4 |
| 30 days | 25.8 | 35.3 |
| 90 days | 12.7 | 35.1 |

The animals contained in a cylindric plastic box with a diameter of 65 mm, were placed in the crystal in such a way that the centre of the animals lay on its central axis The animals were measured within 3 min after injection and at 1 3 7 and 14 days after administration of $^{85}Sr$ and were then sacrificed (except for the controls) The amount of $^{85}Sr$ injected was calculated to give an initial count of 63 000 ± 2 000 cpm

## Results

The results of the measurements of the retention of $^{85}Sr$ in the control group are seen in Table 2 The figures corrected for decay are also given The results of the attempts to influence the retention of $^{85}Sr$ by various agents are summarized in Table 3 The retention on the 7th day as percentages of the initial measurements, is given in Table 4 No correction has been made in this table for the decay of the nuclide during the fortnight since all the groups are treated in the same manner and the effect of decay is less than 9 % after 7 days as shown in Table 2

There was no statistically significant difference between the relatively small primary groups *except in the case of strontium chloride It was therefore con*sidered justifiable to combine the groups in the following way treatment 30 and 10 min before injection of $^{85}Sr$ was designated pre treatment 10 and 30 min after injection early post treatment and at 1 and 24 hours late post treatment

The mean value of the retention of the control groups at 7 days has been used as the standard value with which the results for the treated groups have been compared The results have been statistically treated (as indicated in Table 5) The t value and the significance level are calculated in order to compare the standard retention value of the controls and the retention of the treated group in question

Strontium chloride decreased the retention of $^{85}Sr$ if given as pretreatment, early post treatment or after 1 hour Administration at 24 hours had no effect The greatest and most unequivocal effect was obtained with early post

**Table 3**

*Retention of $^{85}Sr$ after treatment with various agents (percentage of dose administered)*

| Agent | Dose mM/kg | Period of treatment | Days | | | |
|---|---|---|---|---|---|---|
| | | | 1 | 3 | 7 | 14 |
| Controls | | | 65.1 | 51.9 | 43.9 | 37.3 |
| Sr chloride | 2.0 | Pretreatment | 51.7 | 37.0 | 32.0 | 25.3 |
| | | E. post treatment | 51.6 | 34.8 | 28.7 | 23.3 |
| | | L. » | 66.1 | 47.3 | 38.9 | 30.2 |
| Sr lactate | 1.5 | Pretreatment | 62.9 | 45.0 | 35.9 | 29.7 |
| | | E. post treatment | 61.9 | 45.4 | 35.9 | 29.5 |
| | | L. » | 65.5 | 50.9 | 40.3 | 33.2 |
| Sr lactate | 2.0 | Pretreatment | 51.4 | 36.2 | 29.5 | 23.9 |
| | | E. post treatment | 66.2 | 48.5 | 38.9 | 31.0 |
| | | L. » | 58.5 | 38.9 | 35.2 | 27.5 |
| Ca chloride | 1.0 | Pretreatment | 62.8 | 52.1 | 43.1 | — |
| | | E. post treatment | 63.3 | 50.9 | 43.7 | — |
| | | L. » | 64.3 | 52.0 | 43.9 | — |
| Ca lactate | 1.0 | Pretreatment | 82.4 | 66.0 | 52.2 | 39.6 |
| | | E. post treatment | 79.1 | 61.8 | 49.4 | 40.7 |
| | | L. » | 76.7 | 60.0 | 47.9 | 41.7 |
| Ca lactate | 1.5 | Pretreatment | 86.0 | 64.4 | 49.5 | 43.5 |
| | | E. post treatment | 86.8 | 66.4 | 54.0 | 45.8 |
| | | L. » | 80.7 | 65.7 | 56.8 | 47.6 |
| Na lactate | 1.0 | Pretreatment | 71.2 | 43.3 | 44.5 | 36.9 |
| | | E. post treatment | 68.7 | 41.6 | 42.7 | 35.4 |
| | | L. » | 66.7 | 39.0 | 42.0 | 35.0 |
| Na lactate | 2.0 | Pretreatment | 74.9 | 57.6 | 47.1 | 36.7 |
| | | E. post treatment | 71.8 | 54.4 | 45.3 | 34.8 |
| | | L. » | 71.3 | 56.6 | 47.7 | 36.5 |
| Na rhodizonate | 0.3 (about) | Pretreatment | 68.1 | — | 46.2 | 39.4 |
| | | E. post treatment | 68.5 | — | 45.9 | 40.3 |
| | | L. » | 62.1 | — | 40.4 | 35.9 |
| Mg sulfate | 3.0 | Pretreatment | 50.3 | 35.5 | 30.4 | 28.0 |
| | | E. post treatment | 51.9 | 37.1 | 32.7 | 28.9 |
| | | L. » | 61.0 | 34.0 | 37.9 | 33.0 |
| CaNa EDTA | 2.0 | Pretreatment | 63.7 | 52.3 | 41.4 | 31.6 |
| | | E. post treatment | 57.3 | 50.2 | 42.2 | 34.0 |
| | | L. » | 64.6 | 52.[illegible] | 43.7 | 36.3 |
| CaNa EDTA | 4.0 | Pretreatment | 63.2 | 48.9 | 41.3 | 33.3 |
| | | E. post treatment | 63.5 | 48.3 | 41.5 | 33.3 |
| | | L. » | 64.5 | 49.6 | 41.4 | 31.2 |
| CaNa DTPA | 2.0 | Pretreatment | 54.1 | 44.1 | 36.8 | 29.0 |
| | | E. post treatment | 53.1 | 43.3 | 35.9 | 28.5 |
| | | L. » | 59.6 | 47.6 | 37.8 | 30.3 |
| CaNa DTPA | 5.0 | Pretreatment | 57.6 | 42.6 | 36.8 | 28.8 |
| | | E. post treatment | 57.2 | 41.6 | 36.0 | 27.8 |
| | | L. » | — | — | — | — |

**Table 4**

*Retention 7 days after administration of $^{85}Sr$ (percentages of dose administered)*

| Agent | Dose mM/kg | Pretreatment | | Early post treatment | | Late post treatment | |
|---|---|---|---|---|---|---|---|
| | | 30 min | 10 min | 10 min | 30 min | 1 hour | 24 hours |
| Phys saline (controls) | — | 42 7 ± 0 7 | 45 3 ± 1 5 | 43 7 ± 0 8 | 44.2 ± 1.9 | 43.5 ± 1 6 | 44.2 ± 1 7 |
| Sr chloride | 2 0 | 32 0 ± 1 1 | 37 0 ± 1.2 | 29 1 ± 1 0 | 28 4 ± 0 4 | 35 5 ± 1 2 | 42.2 ± 1 6 |
| Sr lactate | 1 5 | 32 8 ± 0 9 | 39 0 ± 1 6 | 35 0 ± 8 9 | 36 8 ± 8 8 | 39 5 ± 8 0 | 41 1 ± 5 7 |
| Sr lactate | 2 0 | 29 6 ± 1 1 | 29 4 ± 1 7 | 38 2 ± 1 0 | 39 6 ± 1.5 | 34 6 ± 1.2 | 36 0 ± 1 6 |
| Ca chloride | 1 0 | 45 4 ± 1 9 | 40 7 ± 1 3 | 41 3 ± 1 5 | 46 1 ± 2 1 | 47 7 ± 2 8 | 40 1 ± 2.6 |
| Ca lactate | 1 0 | 57 6 ± 1 3 | 51 8 ± 1 1 | 49 3 ± 1.2 | 49 5 ± 1.2 | 49 9 ± 8.1 | 45 9 ± 1 6 |
| Ca lactate | 1 5 | 58 1 ± 4 1 | 44 3 ± 5 7 | 54.2 ± 2 3 | 53 7 ± 1 6 | 62 5 ± 4 0 | 51 1 ± 4 1 |
| Na lactate | 1 0 | 45 5 ± 1 7 | 43 5 ± 1 3 | 44 3 ± 1 7 | 40 6 ± 2.5 | 41 7 ± 1 7 | 47 3 ± 2 6 |
| Na lactate | 2 0 | 49 0 ± 1 0 | 45 6 ± 1 7 | 47 5 ± 1 7 | 42 6 ± 0 8 | 47 8 ± 1 9 | 47 6 ± 3 7 |
| Na rhodizonate | 0 3 (about) | 46 7 ± 2 5 | 45 8 ± 1 3 | 48 9 ± 2 6 | 42 9 ± 1 1 | 40 8 ± 2 4 | 39 9 ± 1 9 |
| Mg sulfate | 3 0 | 32 1 ± 1 8 | 28 8 ± 1 6 | 33 2 ± 1 6 | 37 1 ± 1 4 | 35 3 ± 1 5 | 40 4 ± 1 1 |
| CaNa EDTA | 2 0 | 43 1 ± 1 0 | 39 7 ± 2 2 | 44 7 ± 3 0 | 39 6 ± 1 4 | 45 0 ± 1 4 | 42 3 ± 2 0 |
| CaNa EDTA | 4 0 | 44 3 ± 2 8 | 38 3 ± 3 5 | 41 6 ± 1 3 | 41 4 ± 1 4 | 42 1 ± 1 4 | 40 7 ± 2 7 |
| CaNa DTPA | 2 0 | 37 6 ± 1 5 | 35 9 ± 0 7 | 36 3 ± 0 7 | 35 4 ± 1 1 | 38 4 ± 1 6 | 37.2 ± 2 1 |
| CaNa DTPA | 5 0 | 37 9 ± 2 0 | 35 6 ± 1 4 | 34 8 ± 2 0 | 3 1 ± 0 8 | — | — |

treatment As no significant difference between 0 5 1 and 4 mM/kg was observed on the effect of retention 2 mM/kg was used for the complete examination The influence of strontium lactate was also statistically significant but inferior to that of strontium chloride The effect of magnesium sulfate on the retention was of the same order of magnitude as that of strontium chloride The concentration used was 3 mM/kg which appeared to be the optimal dose

$CaNa_3DTPA$ was inferior to strontium chloride and magnesium sulfate in decreasing the retention but of the same order as strontium lactate There was no significant difference between 2 and 5 mM/kg

Calcium chloride had no effect and calcium lactate increased the retention Sodium lactate had no statistically significant effect

Independent of concentrations and times $CaNa_2EDTA$ had no effect on the retention neither had sodium rhodizonate

## Discussion

The results of the present investigation (method II) as well as these results in the light of the previous study (method I) based on the difference between the treated groups and the control groups in the two studies as seen in Table 6, will be considered If the retention value of a treated group is lower than that of the control group the deviation value has been given a negative sign

The results from the control groups in method II show much smaller varia

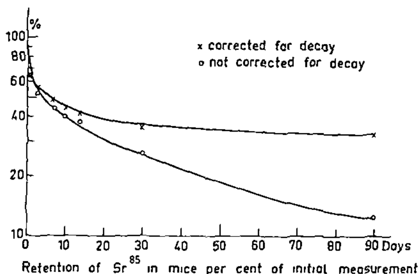



Diagram (see text on p 137)

tions in spite of a lower number of animals in the groups, which indicates that method II as could be expected is more accurate

The control animals in method I showed a significantly higher retention of radiostrontium (47 8 %) than those in method II (43 9 %) The fact that $^{90}$Sr was used in the first and $^{85}$Sr in the second case cannot explain the difference, since in both cases carrier free strontium was used In the first case (CARLQVIST & NELSON 1960) special animals were used as blanks in order to obtain initial radiation values for calculating the retention in the control groups as well as in the treated groups

Among previous attempts to influence the elimination of radiostrontium MACDONALD (1955) CLARK (1960) and CATSCH & MELCHINGER (1959) succeeded in decreasing the skeletal retention of strontium 90 by the injection of inactive strontium salts in rats An effect was evident in their investigations only if the stable strontium was given practically simultaneously with $^{90}$Sr CATSCH & MELCHINGER tried increasing doses of stable strontium and found that the effect was not linear A relative increase in the skeletal retention was observed with high doses

No dose dependent effect of inactive strontium was observed within the dose range investigated in the present study

The present retention values in mice are much lower than the retention of $^{90}$Sr in rats reported by CATSCH & MELCHINGER These authors used, however, strontium 90 chloride and investigated only the retention in the femur

**Table 5**

*Statistical treatment of results*

| Agent | Dose mM/kg | Period of treatment | No of mice | Retention mean ± SE | t values and significance levels |
|---|---|---|---|---|---|
| Controls | 0 5 | | 30 | 43 9 ± 0 6 | — |
| Sr chloride | 2 0 | Pretreatment | 10 | 3[illegible] 0 ± 0 8 | 12 7 |
| | | E post treatment | 10 | 28 7 ± 0.5 | 20 3 |
| | | 1 hour after | 5 | 35 5 ± 1.2 | 66.27 |
| | | 24 hours aft r | 5 | 42 2 ± 1 6 | 0 99 |
| Sr lactate | 1 5 | Pretreatment | 10 | 35 9 ± 1 4 | *5 44 |
| | | E. post treatment | 10 | 35 9 ± 2 1 | 3 704 |
| | | L | 10 | 40 3 ± 1 5 | 2 264 |
| Sr lactate | 2 0 | Pretreatment | 10 | 29 5 ± 0 9 | 13 3 |
| | | E post treatment | 10 | 38 9 ± 0 9 | 4 81 |
| | | L. » | 9 | 35 2 ± 0 9 | *7 98 |
| Ca chloride | 1 0 | Pretreatment | 20 | 43 0 ± 1 2 | 0 67 |
| | | E. post treatment | 19 | 43 6 ± 1 4 | 1 97 |
| | | L. » | 15 | 45 2 ± 2 2 | 0 57 |
| Ca lactate | 1 0 | Pretreatment | 10 | 52 2 ± 0 8 | 8 47 |
| | | E. post treatment | 10 | 49 4 ± 0 8 | 5 79 |
| | | L. » | 10 | 47 9 ± 1 5 | 1 85 |
| Ca lactate | 1 5 | P etreatment | 8 | 49 5 ± 4 4 | 1.25 |
| | | E. port treatment | 10 | 54 0 ± 1 3 | 7 11 |
| | | L. » | 10 | 56 8 ± 3 5 | 3 675 |
| Na lactate | 1 0 | Pretreatment | 10 | 44 5 ± 1 0 | 0 51 |
| | | E post treatment | 9 | 42 7 ± 1 5 | 0 75 |
| | | L. » | 10 | 42 0 ± 1 5 | 1 172 |
| Na lactate | 2 0 | Pretreatment | 9 | 47 1 ± 1 1 | 2 539 |
| | | E. post treatment | 9 | 45 3 ± 1 3 | 1 00 |
| | | L. » | 10 | 47 7 ± 2 0 | 1 87 |
| Na rhodi onate | 0 3 (about) | Pretreatment | 10 | 46.2 ± 1 3 | 1 61 |
| | | E post treatment | 10 | 45 9 ± 1 7 | 1 11 |
| | | L » | 9 | 40 4 ± 1 5 | 2 16 |
| Mg sulfate | 3 0 | Pretreatment | 10 | 30 4 ± 1 3 | 9 44 |
| | | E post treatment | 10 | 32 7 ± 1 0 | *9 57 |
| | | L. » | 10 | 37 9 ± 1.2 | 4 48 |
| CaNa EDTA | 2 0 | Pretreatment | 10 | 41 4 ± 1 3 | 1 84 |
| | | E. post treatment | 10 | 42 2 ± 1 8 | 1 28 |
| | | L. » | 10 | 43 ± 1 2 | 0 15 |
| CaNa EDTA | 4 0 | Pretreatment | 10 | 41 3 ± 2 4 | 1 07 |
| | | E post treatment | 10 | 41 5 ± 0 9 | [illegible] 31 |
| | | L. » | 10 | 41 4 ± 1 5 | 1 59 |
| CaNa DTPA | 2 0 | Pretreatment | 20 | 36 7 ± 1 1 | 5 76 |
| | | E post treatment | 20 | 35 9 ± 0 7 | 8 70 |
| | | L. » | 20 | 37 8 ± 1 3 | 4 27 |
| CaNa DTPA | 5 0 | Pretreatment | 10 | 36 8 ± 1 2 | 5.26 |
| | | E post treatment | 10 | 36 0 ± 1 1 | 6 37 |
| | | L » | — | — | — |

— $p \leq 0\ 05$ — $p \leq 0\ 01$ — $p \leq 0\ 001$

**Table 6**

*Comparison betw en the ashing method I ($^{90}Sr$) and SAC method II ($^{85}Sr$) percentage of dose administered*

| | | Method I | Method II | t values |
|---|---|---|---|---|
| Controls | | 47 8 ± 0 9 | 43 9 ± 0 6 | *3 611 |
| *Difference between treated groups and control groups* | | | | |
| Agents | Dose mM/kg | Method I | Method II | t values |
| Sr chlorid | 2 0 | − 7 1 ± 1 66 | −11 9 ± 1 00 | 2 474 |
| | | −10 9 ± 1 66 | −15.2 ± 0 78 | 2 337 |
| | | − 1 4 ± 1 76 | − 8 4 ± 1 34[a] | 3 153 |
| | | | − 1 7 ± 1 ,1[b] | 0 121 |
| Sr lactat | 1 5 | − 3 9 ± 1 58 | − 8 0 ± 1 5? | 1 864 |
| | | − 5 1 ± 1 92 | − 8 0 ± 2 18 | 0 997 |
| | | 3 1 ± 1 42 | − 3 6 ± 1 62 | 3 116 |
| Sr lactate | 2 0 | − 2 7 ± 2 10 | −14 4 ± 1 08 | 4 953 |
| | | 0 1 ± 2 ?9 | − 5 0 ± 1 08 | 2 016 |
| | | 3 8 ± 1 50 | − 8 7 ± 1 03 | 6 757 |
| Ca chloride | 1 0 | 18 4 ± 2 38 | − 0 9 ± 1 34 | 7 070 |
| | | 19 1 ± 2 29 | − 0 3 ± 1 5? | 7 055 |
| | | 17 4 ± 2 01 | 1 3 ± 2 8 | 5 256 |
| Ca lactate | 1.0 | 13 1 ± ? 94 | 8 3 ± 1 00 | 1 548 |
| | | 11 6 ± 2 29 | 5 5 ± 1 00 | 2 440 |
| | | 9 9 ± 1.84 | 4 0 ± 1 6? | 2 418 |
| Ca lactat | 1 5 | 19 3 ± 2 58 | 8 6 ± 4 44 | ?94 |
| | | 15 0 ± 2 20 | 10 1 ± 1 43 | 1 870 |
| | | 14 0 ± 1.58 | 12 9 ± 3 56 | 0 284 |
| Na lactat | 1 0 | 3 6 ± 1 84 | 0 6 ± 1 17 | 1 3 6 |
| | | 6.2 ± 1 92 | − 1.2 ± 1 6? | ? 937 |
| | | 5 6 ± 1 4? | − 1 9 ± 1 6? | 3 4 8 |
| Na lacta | 2 0 | 13 0 ± 2.38 | ?2 ± 1.25 | 3 6?? |
| | | 8 1 ± 1 92 | 1 4 ± 1 43 | 2 79? |
| | | 5 0 ± 1 58 | 3 8 ± 2 09 | 0 458 |
| CaNa EDTA | ? 0 | − 1 1 ± 2.29 | − ? 5 ± 1 43 | 0 519 |
| | | 4 5 ± 1 58 | − 1 7 ± 1 90 | 2.510 |
| | | 6 ? ± 1 6 | − 0 2 ± 1 34 | *2 89? |
| CaNa EDTA | 4 0 | 11 4 ± 2 75 | − 2 6 ± 2 48 | *3 ?84 |
| | | 3.2 ± 1 84 | − 2 6 ± 1 08 | ? ?73 |
| | | 6 1 ± 1 50 | − 2 5 ± 1.62 | 3 89 |

a — treatment after 1 hour b — treatment after 24 hours − p ≤ 0 05 * − p ≤ 0 0 − p ≤ 0 001

on the second day after administration The retention in the present investigations was generally measured on the 7th day and on the whole animal It may be seen from Table 2 and the diagram that the retention at day 1 and day 3 is 65 and 54 % respectively which however is in better agreement with the results of CATSCH & MELCHINGER

The inactive strontium salts were able to decrease the retention of radiostrontium as in the previous study Strontium chloride was the most effective salt, the effect was still apparent when it was administered at one hour after $^{85}$Sr but not at 24 hours The decreasing effect after one hour could not be shown in our previous study, probably due to the great variations between the groups

Strontium lactate was not as effective as strontium chloride This an ion effect appears especially with early post treatment This effect was significant when calcium chloride and calcium lactate were compared

The an ion effect observed with sodium lactate in the previous study appears this time only as a tendency

The present studies in mice have confirmed the results of previous investigations in rats with regard to the effect of inactive strontium on the deposition of strontium 90

The effect of non radioactive strontium salts is apparently a carrier effect, and as late post treatment has no effect a release of radiostrontium already fixed in the skeleton cannot be expected

The calcium salts had no decreasing effect on the retention of radiostrontium as in the previous study calcium chloride which previously gave a great increase in retention was this time without any effect

The effects of calcium on the retention of radiostrontium (MACDONALD, SPENCER et coll 1956 CATSCH & MELCHINGER) appear to be inconsistent in agreement with earlier investigations The possibility of a systematic error in the previous investigation with regard to the calcium chloride group can of course not be entirely excluded

It was found that $Mg^{++}$ caused a decreased retention of the same magnitude as strontium chloride in accord with MACDONALD CATSCH & MELCHINGER and CLARKE et coll (1959)

COHN & GONG (1953) and VAUGHAN & TUTT (1953) tested mixed calcium and sodium salts of EDTA but reported no effect on the excretion of $^{90}$Sr, which result was confirmed in the present investigations

Contrary to the excellent effects on the retention of plutonium with sodium DTPA no effect was observed on radiostrontium by KRIEGEL & MELCHINGER (1959) and CATSCH & MELCHINGER A significant decrease of about 80 % of the controls was obtained in the present study The sodium calcium salt of DTPA was used however in a concentration ten times higher that that employed by CATSCH & MELCHINGER without any apparent side effects

No decreasing effect of sodium rhodizonate other than that to be expected

was observed, in accord with the results of other investigators (KRIEGEL & MELCHINGER and VOLF 1959) The Na and K salts of rhodizonic acid apparently have the ability of selectively binding strontium, even in the presence in great excess of calcium (LINDENBAUM et coll 1957, 1958)

**Acknowledgement**

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## SUMMARY

The results of the application of a method in which strontium 85 was measured in living animals by means of gamma spectrometry were found to be in good agreement with those of previous attempts to influence the retention of radiostrontium in mice when strontium 90 was used The effects of numerous agents on the retention are reported and discussed

## ZUSAMMENFASSUNG

Die Resultate einer Methode womit Strontium 85 in lebenden Versuchstieren mit Hilfe von Gamma Spektroskopie gemessen wurde zeigten gute Übereinstimmung mit früheren Untersuchungen über die Beeinflussung der Retention des Strontium 90 bei Mäusen Der Einfluss von verschiedenen Mitteln auf die Retention wird erörtert

## RÉSUMÉ

L application d une méthode de mesure du radiostrontium 85 sur des animaux vivants par spectrométrie gamma a donné des résultats en bon accord avec ceux d essais antérieurs pour influer sur la rétention du radiostrontium sur des souris dans lesquels on avait utilisé le strontium 90 Les auteurs signalent les effects de nombreux facteurs sur cette rétention et les étudient

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# COMPUTATION OF DOSES IN DERMATOLOGIC ROTATION THERAPY

by

P RONNE

GREEN JENNINGS & HENDTLASS (1951) worked with a voltage of 50 kV at a focus skin distance of 50 cm to treat large areas of the human skin with a minimum of tube settings WAGNER (1955) and SCHIRREN (1955) have given treatments at focus skin distances of 100 and 200 cm respectively While at a distance of 100 cm it is necessary to use four radiation fields to cover the front as well as the back of a patient SCHIRREN found it sufficient to use one field for each at a FSD of 200 cm A drawback common to the procedures used by WAGNER and by SCHIRREN is that the sides of the patient are insufficiently ir radiated due to the grazing incidence of the radiation

The possibility of applying the techniques of rotation therapy in an attempt to achieve a more uniform distribution was considered A revolving disk was installed in the floor of a treatment room and on this the patient could stand and support himself with his hands on a coupled bar mounted under the ceiling The roentgen tube was fixed with the central ray directed horizontally and intersecting the vertical axis of the revolving disk A Maclett OEG 60 tube was chosen for the treatments, this is provided with a 1 mm Be window at the end of the tube housing and is said to have a more homogeneous field than other tubes for superficial therapy The tube was energized with a Dermopan apparatus and operated at 50 kV 25 mA and a total filtration of 1 mm Be

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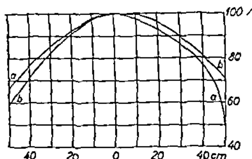



Fig 1 Field inhomogeneity in the 100 cm plane

The dose rate D in the central ray was first measured at a focus distance of 100 cm The direction of the central ray was found visually as the line connecting a point source of light placed 100 cm from the focus and its image in a small mirror placed in contact with the Be window The dose rate measurements were carried out with a Kustner Panzerdosimeter supplied with a Kurzkammer which was adjusted by reference to a parallel plate standard chamber using radiation of the same quality

The percentage variation of the dose in a plane perpendicular to the central ray at 100 cm focus distance is shown in Fig 1 Curve *a* represents the relative dose distribution along a horizontal line while curve *b* is the dose distribution in the vertical direction The tube was mounted with the water inlet directed downwards It can be seen that the irradiation field was most homogeneous in the vertical direction It is possible to draw isodose curves for the entire 100 cm plane with reasonable accuracy (Fig 2) from the curves *a* and *b* of Fig 1

The absorption curves in skin equivalent material for radiation at 100 cm and respectively 200 cm focus distances are shown in Fig 3 In the former case the first HVL was found to be 1 35 mm tissue and the second HVL 1 85 mm tissue

The following simplifications are made to facilitate a calculation of the dose for a full revolution of the patient

1 The dose is calculated only for a horizontal section through the patient at the level of the central ray

2 This section is approximated by an ellipse with the semi axes $b = 12$ cm (from the axis of rotation to the skin surface over the sternum and spine respectively) and $a = 19$ cm (from the axis of rotation to the sides of the thorax)

3 The axis of rotation is placed 115 cm from the focus coinciding with the centre of the ellipse The FSD in the direction of the central ray will then vary from 103 cm (focus sternum and focus spine, respectively) to 96 cm (from focus to either side of thorax)

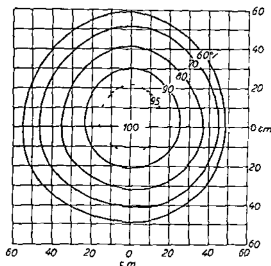



Fig 2 Isodose curves in the 100 cm plane

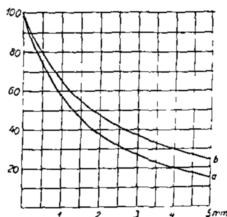



Fig 3 Curves of absorption in tissue equivalent material curve *a* at a focus distance of 100 cm curve *b* at a focus distance of 200 cm

*In Fig 4 $SS_1$ represents the track followed by the xiphi sternum in a rotation of the patient* by $a$ (degrees) from the central ray FO The dose rate received to the sternum in the position $S_1$ is given by

$$d_a = k_1 \; k_2 \; k_3 \; D = k_a \; D$$

where

D is the dose rate at the point of reference C of the central ray FC = 100 cm

$k_1$ is a correction taking account of the inhomogeneity of the field from C to S

$k_2$ is a factor correcting for the decrease of the dose rate from $S_2$ to $S_1$ according to the inverse square law

$k_3$ is a correction factor for the decrease of the dose rate due to absorption in the air between $S_2$ and $S_1$

*To find the correction factors for different values of $a$ it is necessary to calculate* $x$ $y$ and $r'$ in Fig 4 This may be done with the aid of the simple trigonometric formulae

$$x = \frac{100}{115 - 12 \cos a} \; 12 \sin a$$

$$y = \sqrt{115^2 + 12^2 - 2 \; 115 \; 12 \cos a}$$

$$r = \sqrt{100^2 + x^2}$$

Since curve $a$ (Fig 1) is not symmetrical with respect to the central ray an average value of $k_1$ has been used in the table this means that the irradiation of the xiphi sternum is considered to be equal for positive and negative values of $a$

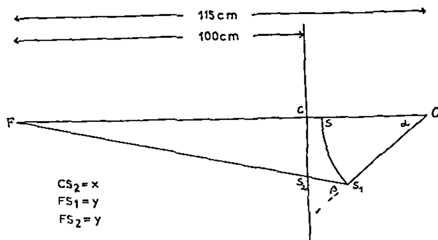
The values of $x$ $y$ and $y$ have thus been calculated for $a = 0 \quad 10 \quad 20 \qquad 80$ and by using these results one finds the values of

$k_1$ from curve $a$ (Fig 1)

$k_2$ from $k_2 = \left(\frac{y}{y}\right)^2$

$k_3$ from curve $a$ (Fig 3)

considering that $(y - y)$ cm air correspond to $(y - y)/80$ mm tissue




F g 4 Geometry of irradiation at sternum α degrees from the central position

The dose for one revolution may be calculated with sufficient accuracy if the time Γ for one turn is divided into 36 sections of equal size for which the dose to the sternum is given by

$$T/36 \quad \frac{d_\alpha + d_{\alpha \quad 10}}{2}$$

The total dose in one revolution will, therefore be $D_0 = \frac{T}{36} \quad 2 \quad (0 5 d_0 + d_{10} + d_{20} +$

$$+ 0 7 d_{80}) = \frac{T \ D}{18} \quad (0 5 k_0 + k_{10} + k_{20} + \qquad + 0 7 k_{80})$$

where e g $k_{10} = k_1 \ k_2 \ k_3$ for $\alpha = 10$ degrees At an angle of $\alpha = 84$ the radiation will strike the sternum tangentially The correction factors k $k_2$ and $k_3$ as well as their product $k_\alpha$ are given in the table for different values of α

If a calculation of the dose at 1 mm depth is also desired $d_\alpha$ must be corrected by a further factor $k_4$ to take care of absorption in a skin layer of thickness z which the radiation has to penetrate If the surface of the skin is considered to be a plane within a small area around the xiphi sternum we have $z = 1/\cos \beta$ where β is the angle of incidence (Fig 4) which can be computed from the relation

$$\sin \beta = \frac{115}{y} \quad \sin \alpha$$

**Table**

*Calculations of dose on sternum focus-axis of rotation 115 cm*

| | k | k | k | k | k = k $k_2$ k | $k_\alpha$ = k $k_2$ k k |
|---|---|---|---|---|---|---|
| 0 | 1 00 | 0 94 | 0 98 | 0 58 | 0 92 | 0 54 |
| 10 | 1 00 | 0 94 | 0 98 | 0 57 | 0 92 | 0 53 |
| 20 | 0 99 | 0 93 | 0 98 | 0 56 | 0 90 | 0 51 |
| 30 | 0 99 | 0 91 | 0 97 | 0 53 | 0 88 | 0 47 |
| 40 | 0 98 | 0 89 | 0 95 | 0 49 | 0 83 | 0 43 |
| 50 | 0 98 | 0 87 | 0 94 | 0 42 | 0 80 | 0 33 |
| 60 | 0 97 | 0 84 | 0 93 | 0 32 | 0 76 | 0 24 |
| 70 | 0 97 | 0 81 | 0 91 | 0 20 | 0 72 | 0 14 |
| 80 | 0 97 | 0 78 | 0 90 | 0 00 | 0 69 | 0 00 |

For the calculated values of z the factor $k_4$ can be read from the absorption curve $a$ in Fig 3 The total correction factor $k_\alpha = k_1\ k_2\ k_3\ k_4$ is then calculated for all values of $\alpha$ and the dose $D_1$ at 1 mm depth may be evaluated by analogy with $D_0$

Similar calculations have been carried out for the sides of thorax, the only difference being that $b$ (= 12 cm) is replaced by $a$ (= 19 cm) An attempt has here been made however to estimate the influence of the curvature of thorax on the thickness of the absorbing layer The difference between the z values found by the two methods is considerable only for larger values of $\alpha$ and $\beta$ A value of z = 44 mm was for example, found by the primitive method, as compared to z = 11 mm with the more exact calculation for $\alpha = 80$ Both of these thicknesses will however only permit a small percentage of the radiation to penetrate to a depth of 1 mm It was consequently found that the depth dose calculated by taking the curvature of the surface into account exceeded the former value by only 2 %

The dose at other points of the elliptical cross section must lie between those at the sternum and at the sides of the thorax These differ by only 10 % Nevertheless a computation was also carried out for a point P of the ellipse the radius vector of which subtends an angle of 45 with the principal axes From the formula of ellipse expressed in polar coordinates

$$\varrho^2 = \frac{b}{1 - \varepsilon^2 \cos^2 v}$$

the distance $\varrho$ from P to the axis of rotation is found to be 14 4 cm since $v = 45$ and $\varepsilon = \sqrt{\frac{a^2 - b^2}{a}} = 0\ 775$ The surface dose may then be calculated with the formulae given above

The angle of incidence is found to be 23 2 degrees when point P of the ellipse is located on the central ray By turning the ellipse in one direction from the central ray ($\alpha$ negative) the angle of incidence will become $\gamma = \beta + 23\ 2$ degrees while for a turn in the opposite direction ($\alpha$ positive) $\gamma = \beta - 23\ 2$ degrees The irradiation will consequently not be symmetrical with respect to the central ray and it will be necessary to calculate the depth dose for each interval of 10 degrees ranging from $\alpha = -60$ to $\alpha = +107$

We then arrive at the following results

D = 150 r/min at 100 cm focus distance

*Surface dose per revolution*

| | | | |
|---|---|---|---|
| Sternum and spine | $D = 0\ 375$ D T | = 56 3 T | roentgen |
| Sides of thorax | $D_0 = 0\ 415$ D T | = 62 2 T | » |
| Point of 45 | ($D_0 = 0\ 383$ D T | = 57 5 T | » ) |
| Mean value | $D = 0\ 395$ D T | = 59 2 T | roentgen |

*Dose in 1 mm depth per revolution*

| | | | |
|---|---|---|---|
| Sternum and spine | $D_1 = 0\ 163$ D T | = 24 5 T | roentgen |
| Sides of thorax | $D_1 = 0\ 182$ D T | = 27 3 T | » |
| Point of 45 | ($D_1 = 0\ 165$ D T | = 24 8 T | » ) |
| Mean value | $D_1 = 0\ 172$ D T | = 25 9 T | roentgen |

T min is the time for a full revolution

Similar measurements and calculations have been carried out with a distance of 215 cm between the focus and the axis of rotation The curves showing the inhomogeneity of the field in the 200 cm plane are found to have almost the same shape as curves *a* and *b* of Fig 1, with the exception that the figures on the abscissa should be doubled From the absorption curve *b* of Fig 3 the first HVL is found to be 1 85 mm tissue and the second HVL 3 0 mm tissue It will be noted that the radiation is considerably more penetrating than in the 100 cm plane

D = 20 r/min at 200 cm focus distance

*Surface dose per revolution*

| | | |
|---|---|---|
| Sternum and spine | $D_0 = 0\ 410\ D\ T = 8\ 2\ T$ | roentgen |
| Sides of thorax | $D_0 = 0\ 433\ D\ T = 8\ 7\ T$ | » |
| Mean value | $D_0 = 0\ 421\ D\ T = 8\ 4\ T$ | roentgen |

*Dose in 1 mm depth per revolution*

| | | |
|---|---|---|
| Sternum and spine | $D_1 = 0\ 215\ D\ T = 4\ 3\ T$ | roentgen |
| Sides of thorax | $D_1 = 0\ 229\ D\ T = 4\ 6\ T$ | » |
| Mean value | $D_1 = 0\ 222\ D\ T = 4\ 4\ T$ | roentgen |

The dose received by skin areas lying above or below the central section will be smaller than the calculated values This is due to the inhomogeneity of the field in the vertical direction and — in the case of the depth dose — to the more oblique incidence as well A calculation of these doses will, however be- come considerably more complicated because of the three dimensional geometry and also due to the fact that an approximation by an ellipse will be rather rough To find an upper limit of the dose per revolution it will generally be sufficient to use those values that can be found by multiplying the previously calculated values for the central section, $D_0$ and $D_1$ with a correction factor $k_s$, which accounts for the inhomogeneity of field in a vertical direction this factor may be read from curve *b* in Fig 1

## Acknowledgement

The help received from Dr H Kopp of the Dermatologic Department is gratefully acknowledged

## SUMMARY

A method of covering large areas of the skin by rotating the patient during the treatment is described The dose per revolution of the patient is calculated for the surface of the skin and for 1 mm depth at distances of 115 cm and 215 cm respectively between the focus and the axis of rotation

## ZUSAMMENFASSUNG

Eine Methode die zur umfangreichen Bestrahlung grosser Hautflachen mit Hilfe von Rotation der Patienten fuhrt wird beschrieben Die Strahlendose an der Oberflache und in 1 mm Tiefe wird fur je eine Umdrehung des Patienten fur einen Abstand Fokus Rotationsachse von 115 cm bezweck 215 cm angegeben

## RÉSUMÉ

L auteur décrit une méthode d irradiation de grandes surfaces de peau par rotation du malade au cours du traitement La dose par révolution du malade est calculée pour la surface de la peau et pour une profondeur de 1 mm à des distances foyer axe de rotation de 115 cm et 215 cm

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# RELATION BETWEEN FIELD SIZE AND TOLERANCE OF RABBIT'S BRAIN TO ROENTGEN IRRADIATION (200 kV) VIA A SLIT-SHAPED FIELD

by

NILS O BERG and MARTIN LINDGREN

It has long been known that the tolerance to roentgen radiation varies with the area and volume of tissue irradiated MOPPET (1931) who used rats appears to have been the first to show that the skin erythema dose increases rapidly with decreasing size of small fields (below 10 mm in diameter) As far as the skin is concerned, the relationship between the erythema dose and tolerance dose respectively, and the area of the field irradiated have been studied by many workers in this field (JOLLES 1939 1941 1953, ELLIS 1942 MACKEE, MUTSCHELLER & CIPOLLARO 1943, GOLDBERG 1944 JOLLES & MITCHELL 1947 and JOYET & HOHL 1955) Various theories and formulae have been suggested to explain this co-variation

The relation between the volume of the irradiated tissue and the tolerance dose of inner organs has however received less attention More precise knowledge of this relation for small areas of the CNS has become urgent since the introduction of stereotaxic radiosurgery of the brain (LEKSELL 1951 1957) Ultrahard radiation provides the best possibilities of analysis in this respect (TOBIAS 1952 LIDEN 1957, LARSSON LEKSELL REXED & SOURANDER 1959) Using conventional radiation BERG & LINDGREN (1958) made a comprehensive

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**Table 1**

*Survey of treatment scheme and data of survival in the different groups*

| Width of slit in mm | Skin dose in r | Fields | Animals | Animals irrad over 2 fields | Number of animals with neur symptoms | Survival in weeks: Range | Survival in weeks: Mean | Deaths from intercurrent disease |
|---|---|---|---|---|---|---|---|---|
| 1 | 18 000 | 5 | 5 | 0 | 0 | — | 52 | 0 |
| 2 | 27 000 | 6 | 6 | 0 | 6 | 1—2 ½ | 1 8 | 0 |
| | 18 000 | 5 | 5 | 0 | 2 | — | 52 | 1 |
| | 13 500 | 5 | 5 | 0 | 0 | — | 52 | 0 |
| | 9 000 | 11 | 8 | 8 | 0? | 14—52 | 42 7 | 2 |
| | 3 000 | 12 | 9 | 9 | 0 | — | 52 | 0 |
| 4 | 9 000 | 5 | 5 | 5 | 5 | 37—52 | 46 8 | 0 |
| | 5 000 | 5 | 5 | 0 | 1 | — | 52 | 0 |
| | 3 000 | 6 | 6 | 6 | 0? | 22—52 | 47 | 1 |
| 6 | 5 000 | 5 | 5 | 0 | 4 | 32—52 | 48 | 0 |
| | 3 000 | 5 | 5 | 0 | 0? | 26—52 | 43 8 | 2 |
| 8 | 3 000 | 8 | 8 | 4 | 1 | 18—52 | 43 5 | 2 |
| 12 | 3 000 | 5 | 5 | 0 | 3 | 32—52 | 48 | 0 |
| | 2 100 | 5 | 5 | 0 | 0 | — | 52 | 0 |
| 30* | 3 000 | 20 | 20 | 0 | 18 | 25—52 | 44 3 | 0 |
| | 2 500 | 10 | 10 | 0 | 6 | 46—52 | 51 1 | 1? |
| | 2 100 | 10 | 10 | 0 | 2 | 39—52 | 50 5 | 0 |
| | 1 700 | 6 | 6 | 0 | 0 | — | 52 | 0 |

* Groups from a previous investigation inserted for comparison

analysis of the late cerebral lesions in rabbit following irradiation of half of the brain The relatively small focus of the apparatus (4 mm) enabled extension of the investigation to include even narrow fields

The present investigation is concerned with the morphology and frequency of delayed radiation lesions in the rabbit s brain following different roentgen doses delivered via a slit varying in width from 12 mm to 1 mm

## Material and Methods

Eighty two rabbits weighing 2 to 3 kg and received in litters of 2 to 10 animals were distributed as equally as possible among the different groups to be irradiated The animals were irradiated under deep urethan anesthesia Table 1 gives slit width, skin dose and number of animals treated in the different

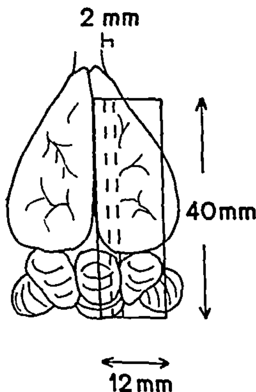



Diagram 1 Position of the 2 mm and the 12 mm slits over the rabbit's brain

groups The experiment was carried out in two series, irradiated at an interval of about one year Some of the animals in the first series died within 3 months from gangrene of one of the legs after injection of urethan in 25 % solution into the thigh These animals were excluded and the brain was not examined histologically In the other series 12 5 % urethan was injected subcutaneously without subsequent complications Each group treated consisted of at least 5 animals

During irradiation the head was carefully fixed in position by 4 clamps placed in a frame with the head gripped infraorbitally and occipitally The slits were 40 mm long and 12 8, 6 4, 2 and 1 mm wide, respectively The central beam was directed towards the middle of the slit The medial border of the slit was placed about 3 mm lateral to the midline of the skull The position of the slits over the rabbit s brain is illustrated in Diagram 1 Lead shielding — 2 mm thick — prevented irradiation of the rest of the animal

The animals were under careful observation and they were weighed regularly After 52 weeks all the surviving animals were bled under anesthesia The brain was fixed in formalin and sectioned systematically in the way described by BERG & LINDGREN (1958) The lesions were noted on standard diagrams (Diagrams 3 to 9) showing the extent of cerebral lesions in representative vertical sections through the brain The animals were killed 52 weeks after irradiation if survival time is not given in the legend The dots indicate vascular lesion and glial cell in otherwise normal tissue the hatched areas denote sub total destruction of cerebral tissue and black areas denote cysts or franc necrosis

*Technical data* Roentgen machine Muller MG 300 kV 200 half value layer 0 93 mm Cu, focus skin distance 250 mm dose rate about 100 r per min, dose control by a Philip s do imeter

The depth dose of the central beam at different widths of the slit was cal

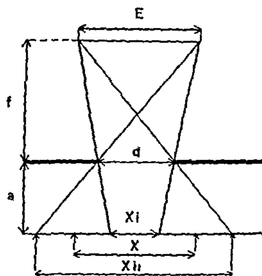



Diagram 2 Geometry of the beam to illustrate calculation of penumbra and effective width of the field $x$ at different depths $a$

- $F$ diameter of focus
- $d$ slit width
- $f$ focus skin distance
- $x$ central beam
- $x$ central beam + total penumbra

culated according to Alsopp (Central Axis Depth Dose Data, Brit J Radiol Suppl 5, 1953) without correction for elongation of the field The unscreened beam and breadth of penumbra at different depths was calculated according to Diagram 2 modified according to Lidén (1957) It is clear from the figure that

$$X_i = d - \frac{a}{f}(E - d) \qquad (1)$$

$$X_{ii} = d + \frac{a}{f}(E + d) \qquad (2)$$

The contribution by the penumbra was therefore

$$X_{ii} - X_i = 2\,\frac{aE}{f}$$

The penumbra at depth, $a$, did not vary with the width of the slit, $d$

According to equation (1), $X_i = 0$, and $d = 1$ mm gives $a = 83.3$ mm This means that a central homogenous field was irradiated through the entire brain even when the narrowest slit was used The position of the lesions in the brain tissue showed that the most deep seated lesions in the brain (21 mm) and in the medulla (34 mm) had been irradiated with a homogenous beam The relation between the homogenous beam and the surrounding penumbra was least favourable for the 1 mm field For the most deep seated brain regions irradiated with this width of slit the homogenous beam was 0 70 mm wide and the width of the penumbra was 0 34 mm on either side This relation was much more favourable for the other lesions observed on irradiation via wider slits (see Table 2)

**Table 2**

*Distribution of different types of lesions and data for most deep seated lesions in the animals*

| Width of slit in mm | Skin dose in r | No of fields | Fields with out lesions | Discrete lesions | Severe lesions | Depth *a* in mm of most deep seated lesion L | Effective width Y of field in L in mm | Depth dose in L in r |
|---|---|---|---|---|---|---|---|---|
| 1 | 18 000 | 5 | 0 | 4 | 1 | 21 | 1 04±0 34 | 10 800 |
| 2 | 27 000 | 6 | 0 | 0 | 6 | — | | |
| | 18 000 | 5 | 0 | 1 | 4 | — | | |
| | 13 500 | 5 | 0 | 5 | 0 | (19) | | 8 600 |
| | 9 000 | 11 | 9 | 2 | 0 | 10 | 2 08±0 16 | *7 100* |
| | 3 000 | 12 | 12 | 0 | 0 | — | | |
| 4 | 9 000 | 5 | 0 | 3 | 2 | (30) | | 4 300 |
| | 5 000 | 5 | 1 | 4 | 0 | 19 | 4 30±0 30 | *3 200* |
| | 3 000 | 6 | 6 | 0 | 0 | — | | |
| 6 | 5 000 | 5 | 0 | 1 | 4 | (28) | | 2 500 |
| | 3 000 | 5 | 3 | 1 | 1 | 18 5 | 6 43±0 29 | *2 000* |
| 8 | 3 000 | 8 | 3 | 1 | 4 | 20 | 8 64±0 32 | 1 950 |
| 12 | 3 000 | 5 | 1 | 0 | 4 | (28) | 12 31±0 50 | 1 850 |
| | 2 100 | 5 | 4 | 1 | 0 | 21 | 13 35±0 45 | *1 700* |
| 30 | 3 000 | 20 | 2 | 2 | 16 | 34 | 38 45±0 53 | *1 500* |
| | 2 500 | 10 | 0 | 0 | 10 | 23 | | 1 700 |
| | 2 100 | 10 | 2 | 6 | 2 | 13 | 33 3 ±0 21 | 1 750 |

The exact distribution of the intensity in the penumbra is not known The effective width, Y of the field was defined as the homogenously irradiated zone + half the penumbra with an accuracy of ± half the penumbra /± ½ (Y —λ)/ This value for Y is surely somewhat too high Calculation for a 2 0 mm slit thus showed a homogenously irradiated central field 1 92 mm in width at a depth of 10 mm and the effective width is given as 2 08 ± 0 16 mm

## Results

Those animals that received 27 000 r via a 2 mm slit deteriorated rapidly they became soporose and all died within 18 days Marked gross cerebral edema with depression of the cerebellum in the foramen magnum was noted as well as a strip showing hyperemia and petechial hemorrhages Microscopic ex amination showed recent necroses with petechial hemorrhages in the irradiated tissue as well as marked edema of the adjacent tissue The changes involved both the grey and the white matter This group was not analysed further

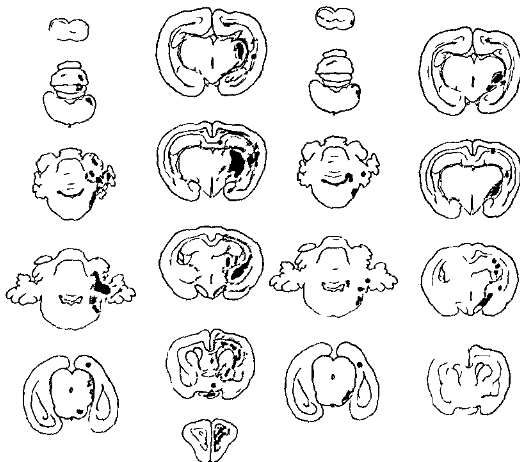


Diagram 3 Dose 3 000 r/12 mm Large necrotic areas mainly in white substance extension of lesion as after irradiation through a 30 mm slit in previous investigation

Diagram 4 Dose 5 000 r/6 mm Mainly well demarcated necrosis in white substance at a depth of about 20 mm This animal died 32 weeks after irradiation

(For explanation of symbols see text p 149 )

In the other groups only few of the animals died The frequency of neurologic signs is given in Table 1 The dominating symptom was 'turning of the head to the treated side (12 animals) A few animals 'walked in circles and had nystagmus and convulsions These symptoms and signs were often followed by emaciation In some animals (1 animal — 18 000 r/2 mm slit, 3 animals — 5 000 r/6 mm slit, 1 animal — 3 000 r/12 mm slit) the loss of body weight might have been due to paralysis of the masticatory muscles, with consequent oblique abrasion of the edge of the teeth and chewing difficulties These animals probably had an injury of nervus trigeminus in the base of the skull

The microscopic picture of the lesions one year after irradiation via narrow fields of varying width was largely the same as that described in detail on 11

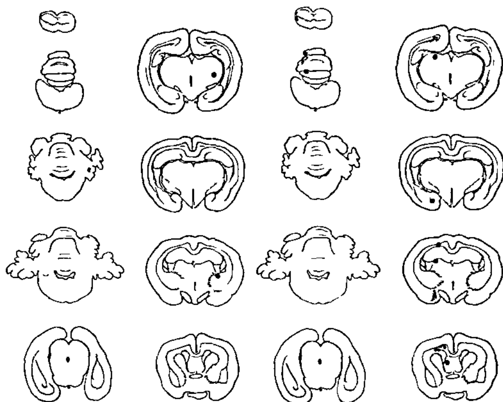


Diagram 5 Dose 5 000 r/4 mm Minimal vascular lesions at a depth of 15 mm

Diagram 6 Dose 9 000 r/4 mm slit to left and 2 mm slit to right Several small lesions in different parts of brain after irradiation via 4 mm slit

(For explanation of symbols, see text p 149 )

radiation of half the brain (slit width 30 mm) in a previous investigation (BERG & LINDGREN 1958 pp 47—62) That investigation included fractionated and single dose irradiation, but only the effects of single doses are referred to here Three types of histologic lesions were recognized namely discrete changes partial destruction and necrosis The occurrence of these changes in the present material is first illustrated

*Discrete changes* in otherwise undamaged brain tissue These consisted of old and recent petechial hemorrhages (Fig 1) endothelial swelling fibrinoid necrosis (Fig 2) or hyalinization of the vessel walls teleangiectasis (Fig 3) and small perivascular glial scars (Fig 4)

*Partial destruction* included partial degeneration of the myelin (Fig 5) or partial loss of nerve cells (Fig 6) and fibrinoid imbibition

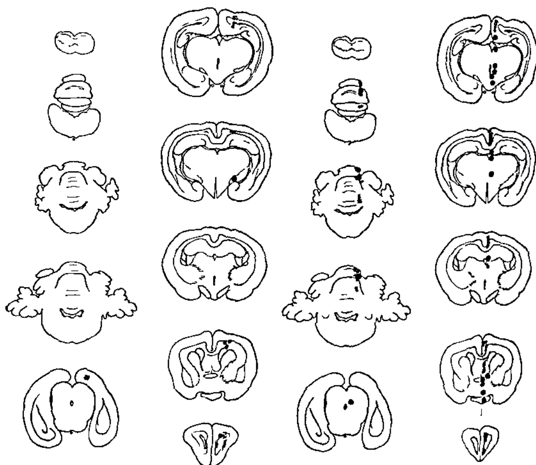


Diagram 7 Dose 13 500 r/2 mm Mainly small vascular lesions in white matter no necrosis

Diagram 8 Dose 18 000 r/2 mm Postnecrotic scars and vascular lesions distortion of field in section through optic chiasm

(For explanation of symbols see text p 149)

*Necrotic changes* Frank necrosis occurred with or without cysts and completely gliovascular destruction of tissue, often with proliferation of atypical glial cells (Figs 7 and 8)

The lesions in those rabbits that were irradiated through a 1 mm and 2 mm slit deserve further illustration In these brains the necrosis did not undergo gross cystic degeneration not even after a dose of 18 000 r After one year the destroyed tissue was, as a rule absorbed and the defect was compressed by the surrounding tissue The final defects were often surprisingly small (Fig 9)

The radiation lesions were readily recognized in the white substance in preparations stained for myelin (Figs 10 and 11) Gliovascular changes were

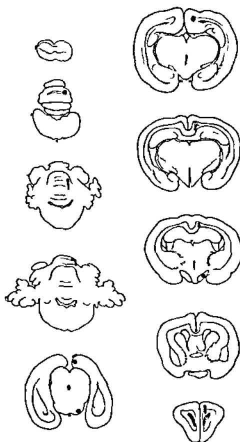


Diagram 9 18 000 r/2 mm Discrete lesions ma nly in white substance (See diagram 7 for comparison)

(For explanation of symbols see text p 149)

often very slight, particula areas close to the slit, i e beam was best defined C *edema and vascular lesions* times seen in deeper parts diated area however The lesions closely resemble thos by a 185 MeV proton beam width (REXED MAIR, S LARSSON and LEKSELL 196

Delivery of large do narrow slits often damag ningeal vessels nearest th radiation Splitting, fatty d and thickening of the vess reduction of the lumina an the surrounding meninges v (Figs 12 and 13)

On gradation of the cording to the above me grees of severity it was dif tinguish between partial compressed severe injury than 4 mm in width (I present investigation th were therefore taken to single group (severe les previous investigations, lesions were almost alwa origin In the cerebral t confined to the capillar distribution of the injuries among the different groups of anim Table 2

Typical examples of the distribution of the injuries in the bra Diagrams 3 to 9 *In all these diagrams the radiation lesions were lized to the irradiated field* Severe as well as discrete lesions w grey substance (cerebral and cerebellar cortex central nucle substance (oval center cerebellar medulla optic chiasm) from Diagrams 3 4 6 and 8 A high frequency of lesions in the had been noted in a previous investigation where a slit widt been used It is evident from Diagrams 5 7 and 9 that eve narrow slits (1 to 4 mm) damaged the white substance more substance after irradiation with marginal doses

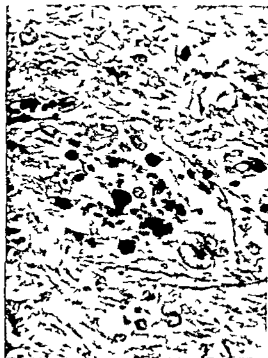


Fig 1 Small capillary hemorrhage with proliferation of glial cells and iron deposits in white substance 13 500 r/2 mm Hematoxylin & eosin × 700



Fig 2 Thickening and fibrinoid degeneration of vascular wall in optic chiasm 18 000 r/2 mm Hematoxylin & eosin × 210

A skin dose of 13 500 r/2 mm (Diagram 7) is a relatively small dose When this dose was exceeded (Diagram 8) widespread lesions in both white and grey substance occurred in most animals (Table 2)

The rabbits irradiated through a 30 mm slit often showed large hemorrhages but those irradiated through the narrow slits did not (Table 3) On the other

**Table 3**

*Frequency of large hemorrhages and tumours in the irradiated animals*

| Group | | | Hemorrhages (large) | | Tumours |
|---|---|---|---|---|---|
| Width of slit in mm | Skin dose in r | | Frequency | Number fatal | |
| 1 and 2 | 13 500 | 18 000 | 0/15 | — | — |
| 4 | 5 000 | 9 000 | 0/10 | — | — |
| 6 | 3 000 | 5 000 | 2/10 | — | 1 malignant glioma |
| 8 | 3 000 | | 1/8 | — | — |
| 12 | 2 100 | 3 000 | 1/10 | — | — |
| 30 | 2 100<br>3 000 | 2 500 | 11/40 | 4 | 1 osteogenic sarcoma |



Fig 3 Recent hemorrhage in tel ang ectatic vessel in oval cent r (depth from skin about 7 mm) 18 000 r/1 mm Hematoxylin & eosin × 43



Fig 4 Glial scar with prol feration of glial cells and endothelial cells 13 500 r/2 mm Hematoxylin & eosin × 480

hand petechial hemorrhages in cerebral tissue were common in all groups (Figs 1 3 and 14) One animal that had received 3 000 r/6 mm slit showed an undifferentiated glioma close to an area of complete gliovascular destruction (Fig 15) No osteogenic sarcomas were seen

## Discussion

*Correlation between width of slit radiation dose and irradiation injury* In an attempt to elucidate these relations the changes noted were analysed in two ways (1) determination of the frequency of injuries in each group as judged by a standardized examination method and (2) determination of the lowest focal doses delivered via slits of varying width that produced morphological changes

1 Diagram 10 gives the distribution of the lesions according to severity in the different groups In this log log diagram the doses given refer to skin doses, and the width of the slit to the width of the beam at the surface of the skin It is obvious that the injurious effect of irradiation decreased markedly with the width of the slit and that the frequency of the lesions decreased with every



Fig 5 Partial destruction of myelin sheaths in white substance of oval center 18 000 r/1 mm Spielmeyer × 43

Fig 6 *Upper region* Vacuoles and glial cell proliferation in white substance *Lower region* Partial loss of nerve cells in the hippocampus 18 000 r/2 mm Hematoxylin & eosin × 83



Fig 6

decrease of the dose The only exception was that seen in those groups in which half the brain was irradiated (width of slit = 30 mm) i e the group from a previous investigation (BERG & LINDGREN 1958, and unpublished experiments) included in Table 1 for comparison

A tolerance index was calculated from Diagram 10 Each discrete lesion was given 1 point, and each severe lesion 3 points The absolute score noted in each group was then converted into percentage of maximum attainable By graphical interpolation and extrapolation the dose expected to give a score of 50 % was calculated for each width of slit For each dose delivered the width of the slit expected to give a score of 50 % was calculated in the same way

This procedure is largely the same as giving the width of the slit and the dose, respectively, that produced necrosis in 50 % of the animals Discrete lesions were included in the score in order to obtain a more reliable index for the groups consisting of only a few animals

The 50 % scores noted are given in Diagram 11 where they are jointed to a curve (curve A) The curve rises markedly with decreasing width of slit, and the curve is S shaped, i e the ascent appears to decrease when the slits are very narrow

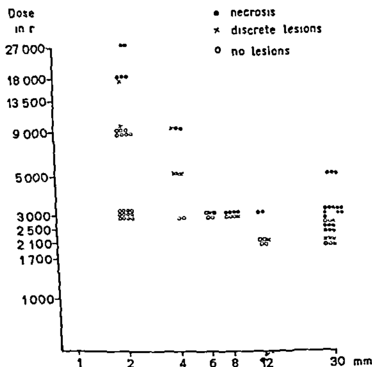



Diagram 10 Results of the morphologic analysis of the rad at on lesions in rabbit s brain in relation to skin dose and width of field plotted in a log log diagram

2 The second procedure, which was used to analyse the relation between irradiation injury and width of the beam, is illustrated in Table 2 which gives the focal doses for those lesions situated farthest from the source of radiation in every group and the effective width of the field at the levels of the lesion

These doses are plotted in the log log diagram (Diagram 11) and the curve (B) thus shows the variation of the tolerance dose with width of slit The maximal width of the field, corresponding to the limit for the entire penumbra, is also given in the diagram Curve B is also S-shaped and a good agreement between the two curves is obvious

This agreement does not exclude a number of sources of error influencing the slope and the shape of the curves The skin doses appear to be fairly accurate For the calculated depth doses (curve B) the error may be about 5 % The increasingly poorer definition of the width of the tissue irradiated with increasing depth is another source of error which is important when narrow fields are used Only 5 animals were irradiated via a slit of 1 mm width The

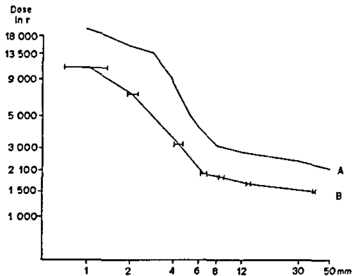



Diagram 11 Correlation between width of field radiation dose and radiation injury in rabbit s brain *Curve A* Tolerance index based on frequency of lesions after irradiation with a given dose (skin) through a given width of slit *Curve B* Lowest focal dose giving morphologic lesions in relation to effective width of field for different groups of animals

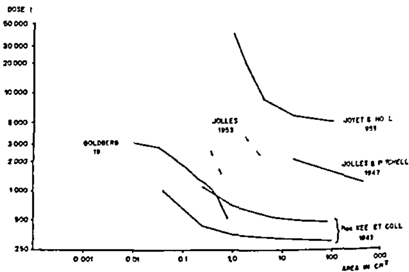



Diagram 12 Area factor for skin tolerance accor l ng to l terature JOYET and HOHL used fractionation of dose (18 sessions in 22 days) The other curves are based on s ngle d se irradiati n



Fig 7



Fig 8



Fig 9

Fig 7 Complete destruction of tissue with proliferation of atypical glial cells 3 000 r/f mm Hematoxylin & eosin × 180

Fig 8 Cortical scar with vacuoles and moderate gliosis 18 000 r/2 mm Hematoxylin & eosin × 83

Fig 9 The central edematous zone with microcysts represents the compressed irradiated field 18 000 r/2 mm Hematoxylin & eosin × 43



Fig 10 Vertical sections through rabbit brain in myelin impregnation The extension of the scar (arrow) is clearly seen on comparison of the two halves of the brain (see also fig 11) 18 000 r/2 mm width × 8

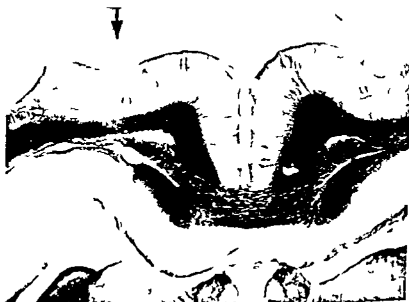


Fig 11 Preparation as in fig 10 from another rabbit The scar is situated further from midline a cortical scar is seen (arrow) the cystic spaces are not true cysts but dilatations of the lateral ventricle on the base of contraction of the scar 18 000 r/2 mm width × 8

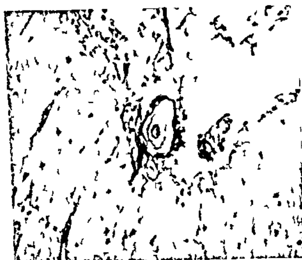


Fig 12 Onion like fib osis and thickening of the wall of an arachno dal vessel 18 000 r/2 mm width v Gieson stain

focal dose found surely exceeds the tolerance dose because all the animals showed injuries The lowest focal dose for this width was not stated

The use of wider slits is accompanied by a different source of error With slits more than 8 mm wide part of the lateral border of the slit lies outside the brain and then adjacent tissue is included in the irradiated field The brain is broadest about 34 mm (in cerebellum) so that when a 30 mm slit is used over half of the brain, only about 17 mm brain tissue is irradiated but at the same time heterogenous tissues of bone, ears cartilage, muscles and skin are included It is not known to what extent irradiation of these tissues might influence the results It is, however obvious that the lower limbs of the curves are relatively well defined whether the effective width of the slit is 17 mm or 30 mm (Diagram 11)

Even the use of a rectangular field instead of an ideal circular field may impair the accuracy of the dose levels of the curves (JOLLES and MITCHELL 1947) Despite these sources of error the following conclusions appear to be warranted

The two curves are based on different types of morphological changes Curve A shows largely the frequency of necrosis in the cerebral tissue and curve B the frequency of discrete small lesions of vascular type Most of the changes are confined to the capillaries The fact that the curves are of the same shape may support the assumption that also necrosis develop from primarily vascular injuries This is supported still further by morphological observations of SCHOLZ 1934 RUSSEL WILSON & TANSLEY 1949 BERG & LINDGREN 1958



Fig 13 Fat *metamorphosis in* vascular wall of arachnoidal *vessel Slight cellular prolifera* tion and abundant fine fat droplets Scarlet R stain 480



Fig 14 Marked *destruction of tissu* and vascular changes along the wall of the third ventricle *in the* center of the field partial or compl te destruction? *18 000 r/2 mm H matoxylin & eosin* 43

and others Large doses however, cause complete destruction of the tissue Such de truction has been observed and interpreted as a primary injury of the nervous tissue (ARNOLD, BAILEY & LAUGHLIN 1954, SCHUMMELFEDER FB SCHNER, BERGEDER & KROGH 1961) Since the capillaries appear to be the most radiosensitive structures in the brain and since extensive diffuse capillary injury to the CNS *invariably results in necrosis their experiments* do not warrant any definitive conclusions concerning the sensitivity *of the nervous* structures

A recent publication by LARSSON *(1960) on the blood brain barrier in early* stages of necrosis following irradiation with 185 MeV proton *beam of 3 mm* diameter are of interest 10 000 rad produced no necrosis within an observation period of max 162 days while *20 000 rad produced necrosis in all the animals* that survived 11 to 14 days His analysis suggests that the injury to the capil laries occurs before and is probably the direct cause of severe damage to the parenchyma

ZEMAN CURTIS, GEBHARD & HAYMAKER (1959) using deuteron beams noted that the dose required to produce histologic lesions in mouse brain was between

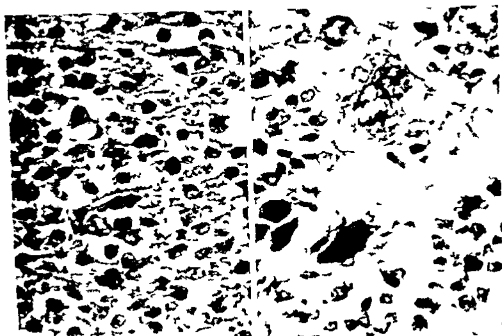


Fig 15 Different parts of an undifferentiated glioma with occasional giant cells 3 000 r/6 mm The tumour was situated close to an area of radiation necrosis with marked proliferation of atypical glial cells (see fig 7 from same animal) Hematoxylin & eosin × 710

15 000 rad and 30 000 rad with a beam 1 mm in diameter With microbeams 25 μ in diameter the threshold dose was approximately $10^4$ rad They concluded that microbeams cause a predominantly direct radiation injury to the brain substance because vessels were only occasionally located within the beam path Furthermore the lesions were sharply delimited and did not follow any vascular distribution pattern Their results are based on observations 24 days after exposure and delayed vascular lesions after exposure to doses below the threshold doses cannot be excluded

*Analysis of shape of curves* The relation found between the tolerance dose and field size was not reliable enough to serve as a basis for mathematical analysis but the shape of the curve can be discussed in more general terms Ionizing radiation initially produces both reversible and irreversible changes The recovery of reversible changes is a process presumably dependent on various accelerating and inhibitory factors LAMARQUE 1942 JOLLES 1950 TOBIAS et coll 1952 JOVET & HOHL 1955 and BACQ & ALEXANDER 1955 have discussed the importance of the formation of toxic substances following irradiation If these

substances are diffusible into adjacent non irradiated tissues, the shape of the tolerance curve will vary considerably with the volume of tissue into which such substances can diffuse JOVET & HOHL used a diffusion model and found good agreement between the expected and observed values for variation of the skin tolerance with the volume of tissue irradiated within field sizes of 1 to 100 $cm^2$ The steep rise of our curves found on reduction of the width of the slit from 12 to 4 mm is also compatible with the existence of a diffusion process Diffusion processes may thus influence recovery after irradiation but the experiments teach nothing of the direction of any such diffusion

DEVIK (1957) has clearly shown that recovery of irradiated epithelial cells in the skin of mice is dependent upon substances diffusing from non irradiated to irradiated cells and such substances may be assumed to be active also in brain tissues

According to the diffusion theory the tolerance dose for irradiation of very small fields should be extremely high But as is apparent from the curves this is not so With a field width of 2 mm the curve showed an initial tendency to flatten This may be explained in different ways Thus, on irradiation with these large doses the irradiation time was so long (max 3 hours) that it could disturb the course of the curve the biological substrate may change and/or the permeability to diffusible substances may increase The fact that protective substances from surrounding tissues may be available only to a certain extent, might also be of significance

We feel however, that some other factor is of decisive importance The recovery phenomenon can restitute only part of the initial changes following irradiation Sooner or later a dose may be achieved where the irreversible part of the radiation changes dictates the shape of the curve The results of ZEMAN et coll (1959) indicate however, that the inverse relationship between radiosensitivity and tissue volume exposed holds for microbeams (25 $\mu$ diameter)

*Area factor for skin and brain* The skin seems to be the only tissue studied in details for the area factor (JOLLES & MITCHELL 1947, LLLIS 1942 JOLLES 1953 GOLDBERG 1944 MACKEE et coll 1943 JOVET & HOHL 1955 and others) There is general agreement that the tolerance varies inversely with the size of the field A graphical demonstration of a number of observations reported in the original papers is given in Diagram 12 in log log scale This diagram covers fields of varying shape and size from 150 $cm^2$ down to 0 01 $cm^2$ None of the investigations include a study of such variation in field size as to produce an S shaped curve If values forming the basis of the curves given by GOLDBERG and by MACKEE et coll are combined, however, they would give an S shaped curve for the skin

In the present investigation an S shaped curve was found for the brain With a modification of the experimental conditions it might be possible to demonstrate an S-shaped curve also for the skin in one and the same experiment

## SUMMARY

The relation between field size and tolerance of rabbit s brain to roentgen irradiation via slit shaped field 12 mm to 1 mm wide has been studied Single skin doses between 2 100 r and 27 000 r were given After 52 weeks the morphology of the lesions was analysed The frequency of injuries as well as the lowest focal dose which produced lesions were determined The effect of irradiation decreased markedly with reduced width of slit The resulting curves for the occurrence of necrosis and for discrete lesions are both S shaped The shape of the curves is discussed especially the influence of diffusion processes Published data on the area factor makes it likely that the tolerance curve for the skin will be S-shaped too

## ZUSAMMENFASSUNG

Der Zusammenhang zwischen der Feldgrosse und der Toleranz des Kaninchengehirns gegenuber Rontgenbestrahlung mit Feldern von 12 mm bis 1 mm Spaltbreite ist studiert worden Einzeitbestrahlungen mit Hautdosen zwischen 2 100 r und 27 000 r wurden ge geben Die Morphologie der strahlenbedingten Hirnveranderungen wurde 52 Wochen nach der Bestrahlung analysiert Die Frequenz der Schaden sowie die niedrigste Herddosis welche einen Schaden hervorrief wurden bestimmt Die Wirkung der Bestrahlung nahm deutlich mit Verminderung der Spaltbreite ab Die sich ergebenden Kurven fur das Auftreten von Nekrosen sowie von diskreten Veranderungen sind S formig Die Form der Kurven wird diskutiert insbesondere der Einfluss von Diffusionsprozessen Bereits veroffentlichte Ober flachenfaktoren machen es wahrscheinlich dass die Toleranzkurve auch fur die Haut einen S formigen Verlauf hat

## RÉSUMÉ

Les auteurs ont étudie l influence des dimensions du champ sur la tolérance du cerveau de lapins à l irradiation roentgen par un champ en forme de fente de 12 mm sur 1 mm de large Ils ont donné des doses uniques de 2 100 r a 27 000 r Ils ont étudié la morphologie des lésions au bout de 52 semaines Ils ont détermine la fréquence des lésions ainsi que la plus petite dose focale ayant causé des lésions L effet de l irradiation décroit beaucoup quand on réduit la largeur de la fente Les courbes d apparition de la nécrose et de lésions discrètes ont toutes deux une forme en S Les auteurs étudient la forme de ces courbes et en particulier l influence des processus de diffusion Il est vraisemblable d après les données publiees sur le facteur surface que la courbe de tolérance de la peau a aussi une forme en S

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# COBALT, COPPER AND IRON IN ANEMIA ASSOCIATED WITH RADIOTHERAPY OF TUMORS

Preliminary communication

by

EINO AUTIO and JOUKO SAIKKONEN

One of the main problems in the treatment of malignant diseases by radio therapy is the protection of healthy tissue from the injurious effects produced by irradiation The hematopoietic system is particularly sensitive to ionizing radiation (WARREN & BOWERS 1950) and its reactions must be continuously followed Leukocytes especially lymphocytes are the cells most affected although the erythroblasts are almost equally susceptible (BLOOM & BLOOM 1947) and anemia resistant to any kind of treatment may develop Moreover since anemia is often associated with many forms of malignant tumors the management of such cases during radiation therapy may be difficult

Cobalt has been used in various anemias resistant to iron vitamins and liver extract These conditions were briefly summarized by ROTHLIN et coll (1956) who stated that cobalt medication is indicated in anemia due to infection rheumatoid arthritis myxedema nephrosis tumors and leukemia as well as in hemolytic anemia They furthermore recommended the use of cobalt simultaneously with copper and iron These three metals are all included in the compound CCF 37 (Sandoz AG Basel) which is supplied in the form of tablets containing 5 mg cobalt 0 5 mg copper and 22 mg iron These tablets

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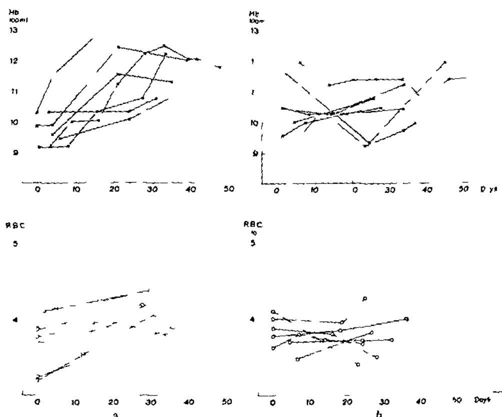



Fig 1 Diagrams showing the erythrocyte counts and hemoglobin values respectively in 7 patients with carcinoma of the breast treated a) with CCF 37 tablets, b) with Ferronicum

have been tested by NORDENSSON (1961), who obtained good results in certain chronic anemias resistant to iron

The erythropoietic effect of cobalt in many animal experiments has been shown to be remarkable Anemia produced by a diet low in protein (ORTEN & ORTEN 1945) and anemia following hypophysectomy (CRAFTS 1952) may be reversed to polycythemia by cobalt SAIKKONEN & MARTTINEN (1963) demonstrated that erythropoiesis in rats may be reactivated by cobalt after sublethal total body roentgen irradiation, the rats were given 250 or 350 r in a single dose and afterwards treated with daily cobalt injections Cobalt treated animals showed a rapid recovery of erythropoiesis in contrast to the controls which were similarly irradiated

These animal experiments inspired the present investigation of the value of cobalt in the treatment and prevention of anemia associated with radiotherapy of malignant tumors

*Material and Methods* The patients were of both sexes and had various malignant tumors Carcinoma of the lung and breast were the most common

conditions but certain other malignant growths were also included in the series These latter included carcinoma of the larynx, tonsil and urinary bladder, hypernephroma ganglioneuroma, reticular cell sarcoma and malignant goitre All except four patients were treated with roentgen rays One patient with carcinoma of the lung one with carcinoma of the urinary bladder and one with reticular cell sarcoma were treated with tele $^{60}$Co, in addition one patient with carcinoma of the tonsil received tele Ra

In carcinoma of the lung the roentgen treatment was generally given to 5 fields of 8 × 10 cm, factors 230 kV 15 mA and 1 mm Cu filter The daily skin dose was 350 r and a total tumor dose of 5 000 r was usually reached in approximately 40 treatments In carcinoma of the breast the same kind of irradiation was administered to 4 fields of 10 × 5 cm, 6 × 15 cm, 8 × 10 cm and 20 × 24 cm The daily skin dose was 350 r but the largest field received only 300 r The average total amount of irradiation was 2 450 r to the skin, the average period of treatment being 29 days

Carcinoma of the lung was also treated with tele $^{60}$Co, 300 r being given at 57 sessions to fields of 6 × 8 cm Carcinoma of the bladder and reticular cell sarcoma were both treated 36 times with 300 r to field areas of 8 × 10 cm Carcinoma of the tonsil received tele Ra treatment 19 times in doses of 732 r

The patients were divided into two groups without reference to the diagnosis and any previous operation Metastases and other changes produced by the tumor had no influence on the basis of division Only those who gradually deteriorated during the period of treatment were disregarded There were three such progressions in the whole material

CCF 37 tablets were administered to the first group of patients daily during the period of irradiation The other group was given only iron in the form of Ferronicum (Sandoz AG) tablets which contain the same amount of iron (22 mg) as CCF 37 tablets but no cobalt or copper Four tablets of CCF 37 or Ferronicum were usually administered daily but in a few exceptional cases 6 tablets were given The anemia treatment was generally started at the same time as the radiotherapy or some days later Red cell and leukocyte counts and hemoglobin values were checked in the usual way

## Results

The changes in blood values during radiotherapy are presented graphically Since carcinoma of the breast and the lung are the commonest conditions in this material each of these is treated separately the few other tumors are treated together

Patients with carcinoma of the breast are represented in Fig 1, in which 1a shows the erythrocyte count and hemoglobin values in 7 *patients treated* with CCF 37 and 1b the same values in 7 patients who received *Ferronicum* There appears to be a significant difference between these groups In all but

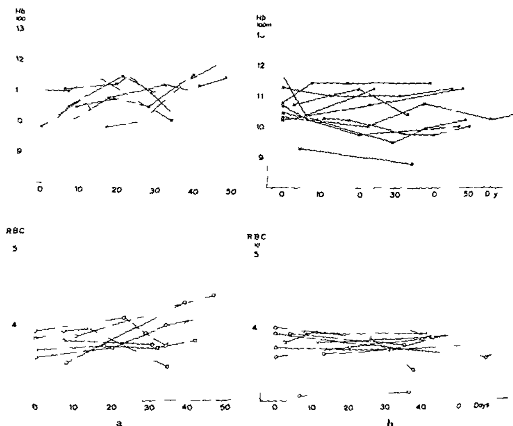



Fig. 2. Diagrams showing the erythrocyte counts and hemoglobin values respectively in 7 patients with carcinoma of the lung treated a) with CCF 37 tablets b) with Ferronicum

one patient treated with CCF 37 a marked elevation of the blood values is evident, in the one patient the values remained at the same level during the treatment. *Ferronicum* was less effective. There was a lowering of the erythrocyte count and hemoglobin in two patients, and in the others the values remained practically constant or a slight elevation occurred. This was however small as compared with the elevation produced by CCF 37.

Fig. 2 represents the patients with carcinoma of the lung, 7 were treated with CCF 37 (Fig. 2a) and 10 with Ferronicum. The corresponding blood values are given in Fig. 2b. In 5 of the 7 patients CCF 37 produced an elevation of the hemoglobin and the erythrocyte count. In one patient the values remained unchanged and in one a lowering was seen. The *Ferronicum* treatment was again less effective. An elevation was evident in only 3 patients and in one the values remained at the same level during the treatment. Impairment was observed in 6 patients.

Other tumors form a miscellaneous group and are collected in Fig. 3, with the patients treated with CCF-37 in 3a and those treated with Ferronicum

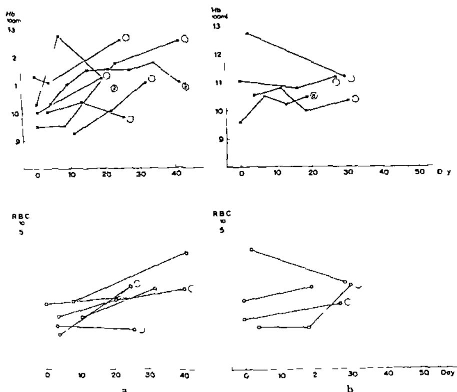



Fig 3 Diagrams showing the erythrocyte counts and hemoglobin values respectively in a miscellaneous group of patients treated a) with CCF 37 tablets b) with Ferronicum The numbers at the curves indicate the kind of lesion 1) carcinoma laryngis 2) carcinoma tonsillae 3) hypernephroma 4) carcinoma visicae urinalis, 5) ganglioneuroma 6) sarcoma reticulocellulare 7) carcinoma thyreo deae 8) tumor giganto cellulare

in 3b The diagnosis is indicated beneath each curve by a number the meaning of which is given beneath the figure Despite the heterogeneity of these tumors and the differences in the radiotherapy the effect of CCF 37 seemed to be superior to that of Ferronicum

The leukocyte count was followed in every patient and the development of moderate leukopenia during the radiotherapy was a constant finding No significant difference in this respect was observed between patients treated with CCF 37 and Ferronicum

The series is comparatively small and more detailed separation of the different types of cases is difficult so that no attempt was made to calculate relative values The curves themselves suggest an advantage of CCF 37 over Ferronicum

Practically no harmful side effects were observed during the treatment. Only one patient treated with CCF-37 had gastric symptoms, these were not severe and may possibly have been an indication of radiation sickness. Six tablets of CCF 37 daily seemed to be more effective than four and the three patients who received this larger dose seemed to tolerate it without difficulty. No further effect was obtained by increasing the dose of Ferronicum to 6 tablets daily.

## Discussion

Many etiologic factors are involved in the development of anemia in patients with malignant tumors subjected to radiotherapy. The role of the tumor, and the secondary changes produced, must first be considered. The injurious effect of ionizing radiation on the bone marrow is also of primary importance. It is not always easy to decide which is the main factor responsible. Many of the patients in the present material were anemic prior to any kind of irradiation. When radiotherapy was started a gradually developing leukopenia and, in some patients, anemia indicated damage to the bone marrow. Both the tumor and the irradiation must therefore be evaluated as etiologic factors in the present series.

The results clearly indicated that cobalt, copper and iron administered simultaneously had a more favourable effect than iron alone on the erythrocyte count and hemoglobin. It was shown in animal experiments by SAIKKONEN & MARTTINEN (1963) that cobalt given alone is capable of reactivating erythropoiesis after radiation injury; it may therefore perhaps be concluded that cobalt may be useful in the treatment of anemia produced by ionizing radiation. The need of iron is self evident but the part played by copper is not so clear. It may be that the optimal effect of cobalt on the anemia produced by irradiation cannot be obtained until some copper is present, as in other conditions (ROTHLIN et coll. 1956). This question cannot be answered from the results of the present preliminary study. It seems, however, that cobalt plays the main role in promoting red cell production.

It must be emphasized that cobalt is a toxic substance and little is known about its mode of action, facts that restrict its general exployment. Many side effects may occur and include disturbances of growth, anorexia and vomiting, claudication and angina pectoris, and the development of goitre (REINOLD 1958). Relatively large doses of cobalt reduce the weight of test animals (STANLEY et coll. 1947) and produce adrenal hyperplasia (FISHER 1958), other stress reactions as well as porphyrinuria also occur (SAIKKONEN 1959). Much depends on the dosage, however, and it seems that a polycythemic reaction is not desirable during the treatment. It is too early to recommend the general use of cobalt but the results are promising and indicate that there are new possibilities of stimulating the bone marrow after radiation injury.

## Acknowledgement

The authors are greatly indebted to Mr Konradin Kreuzer of Sandoz AG Basel for placing CCF 37 and Ferronicum at their disposal

## SUMMARY

Patients with carcinoma of the lung and breast and certain other malignant tumors were treated with cobalt copper and iron during radiotherapy to prevent anemia One group of patients was given the full treatment while the other group received only iron The effect of the three substances given together was superior to that produced by iron alone

## ZUSAMMENFASSUNG

Patienten mit Karzinom der Lunge Mammakarzinom und anderen malignen Tumoren wurden wahrend der Tiefenbestrahlungsbehandlung mit Dosen von Kobalt Kupfer und Eisen behandelt um Anaemie zu verhindern Eine Gruppe erhielt alle diese Elemente wahrend eine andere Gruppe nur Eisen bekam Die erste Gruppe zeigte bessere Resultate als die Gruppe die nur Eisen erhielt

## RÉSUMÉ

Des malades atteints de cancer du poumon ou du sein ou de certaines autres tumeurs malignes ont subi au cours de la *radiothérapie un traitement* par le cobalt le cuivre et le fer pour prévenir l anémie Un groupe de malades a reçu le traitement complet et l autre seulement le fer L effet de ces trois corps administrés simultanément a éte supérieur à celui du fer seul

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# PRESERVATION OF OVARIAN FUNCTION IN EARLY CERVICAL CANCER AFTER SURGICAL LIFTING OF THE OVARIES AND RADIATION THERAPY

by

CARL KREBS N BLIXENKRONE MOLLER and VIBEKE MOSEKILDE

The preliminary results obtained in our efforts to preserve ovarian function in young women with early cervical cancer were published five years ago (3, 4) The patients were first subjected to an operation in which the ovaries were lifted up from their normal site in the lesser pelvis and fixed as high as possible in the abdomen great care being taken in leaving the blood supply intact Radiation therapy was given in the usual way after healing of the operation wound

Loss of ovarian function interferes so seriously with the life of young women that great effort should be made to avoid its occurrence On the other hand, the prognosis of advanced cervical carcinoma is so grave that the paramount consideration must be to give as effective treatment as possible

BATTEN & BROWN (1956) reported a case in which an attempt was made to preserve ovarian function by ensheathing the ovaries in lead shells before radiation therapy was administered A large number of cases has also been described in which surgical removal of the uterus was performed, while one or both ovaries were retained One of the first reports on this type of operation was published in 1958 by MCCALL, KEATY and THOMPSON of Louisiana

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An analysis of the results obtained in patients treated since 1949 is presented in this paper It is accompanied by a brief description of the surgical technique and an estimation of the radiation dose delivered to the ovaries in their normal positions and when lifted and fixed surgically as far away from the uterus as possible

The first operations were performed in 1949—1950 but there was some hesitancy to continue the therapeutic experiments until it was seen how the first patients fared In view of the experience gained in hormone dependent genital cancers involving for example the breast or prostate, there was doubt as to what effect the preserved ovarian function and the continued production of ovarian hormones would have on the prognosis of carcinoma of the cervix uteri if the experiments proved successful It was essential to establish whether a preserved ovarian function would be beneficial detrimental to the result of treatment of cervical cancer, or without significance

Nine of the first patients of 1949—1950 in stage I and under 40 years were given radium therapy alone after surgical ovarian lifting Eight were alive after 7 years without signs, while recurrence in the ninth shortly after the termination of treatment was followed by death within the first 12 months Menstrual function was preserved in 6 of these 8 patients one became pregnant but abortion *occurred at the third month*

It may be mentioned for comparison that during the preceding two years (1948—1949) a total of 24 patients under 40 years of age with cervical carcinoma stage I had been treated with combined radium and roentgen irradiation at the Radium Centre Eighteen of these were alive after 6 years while 6 had died After the lapse of 7 years another patient had died and the growth had recurred in *one A cure was thus obtained in two thirds of cases (in 16 out* of 24) In none of these patients was the menstrual function preserved

Ovarian lifting was also performed in six patients in stage II and in three patients in stage III These were given combined radium and roentgen treatment The beam was as far as possible directed to the parametrium in an attempt to avoid irradiation of the ovaries Menstrual function was not preserved in any of these *patients*

Of the 6 patients in stage II and the 3 in stage III 4 and 1 patients respectively were well and alive after 7 years These figures are small but they do not seem to suggest that lifting of the ovaries reduces the possibility of cure

Inferior midline laparotomy was performed following a complete clinical examination The ligament of the ovary was divided and the ovary with the infundibulo pelvic ligament was mobilised care being taken to leave the blood supply intact The ovary was then lifted and sutured to the margins of a small incision in the parietal peritoneum of the psoas muscle or retroperitoneally to this muscle so that the ovary occupied a position above the ileopectineal line The distance between the growth in the portio and the lower pole of the ovary was usually 13 to 15 cm in a few cases up to 18 cm The fallopian tube

was removed only in a few cases, and usually if it presented signs of chronic inflammation.

Unilateral lifting of the ovary was performed in 7 and bilateral lifting in the remaining cases. Bilateral ovarian lifting has invariably been performed since 1957—1958.

Radium therapy was instituted five to eight days following the operation. Such treatment given in the usual manner will deliver about 3 600 r in 24 hours to the normally placed ovaries. If, as in the present series, the ovaries are moved a distance of about 14 cm the dose will be reduced to about a fortieth, i.e. to about 90 r in 24 hours.

The treatment was resumed in 1957 following a survey of the 1949—1950 series, and an analysis of the entire series is now presented.

Many questions arise in the treatment of young women for carcinoma of the cervix uteri. The general physical condition of the patient must be carefully considered and attention given to the menstrual function and the sex life as well as to the condition of the vagina. Two interesting studies on osteoporosis published by MEIGS (1958) and FRASER & KING (1958, p. 388 should be mentioned at this stage. These authors concluded that abolition of ovarian function results in osteoporosis 15 to 20 years later. A woman undergoing castration at the age of 20 will, when 40 years old, have advanced in bone age to 60 or 70 years.

## Clinical series (1957—1958)

A total of 35 women, whose ages ranged from 23 to 39 years, were treated with bilateral lifting of the ovaries followed by radium irradiation alone. Recurrence was recorded in 10 cases, or 28.5 %.

This figure was compared with the frequency of recurrence calculated after the same observation period in patients of the same age group from the immediately preceding five year period. This was 32.8 % (i.e. 23 out of 70). In spite of the fact that these 70 patients had been given combined radium and roentgen treatment, the percentage of cures obtained after ovarian lifting and radium irradiation does not seem to have been reduced.

Among the 10 patients with recurrence after ovarian lifting, malignancy was evident in two after childbirth (which is always a serious complication), a

*Ovarian lifting*

35 patients, 10 recurrences

| | Recurrence % |
|---|---|
| 1 died within first 9 months | 3 |
| 1 » » 10 » | 6 |
| 1 » » » 3 years | 9 |
| 7 alive by 3 years with recurrence | 28.5 |

*Control series*

70 patients, 23 recurrences

| | Recurrence |
|---|---|
| 2 died within first 3 months | 3 |
| 2 » » » 6 » | 5.7 |
| 8 » » » 12 » | [illegible] |
| 7 » » » 2 years | [illegible] |
| 3 » » 3 » | 37.8 |
| 1 death has subsequently occurred | |

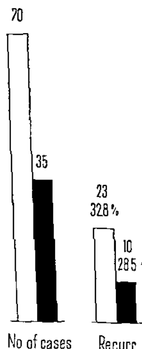



Fig 1 Number of patients and of recurrence in the control series (Ra + roentgen) (white columns) and in patients pre treated with ovarian lifting (+ roentgen) (black columns)

third patient was in stage II and a fourth had a strong familial predisposition (her father and a sister had died of cancer)

These observations may very well serve as a pointer indicating the type of patient in which radium therapy alone will not be sufficient

A more detailed survey of the times of recurrence within the first three years in the two groups is given below

It is possible that some of the patients in the control series classified as stage I had more advanced growths Ovarian lifting was actually performed in 37 patients but two were excluded because operation revealed that the condition was far more advanced than had been assumed at the vaginal examination These figures suggest that the margin of error in vaginal examination performed even by experienced examiners may be about 5 %

*Menstruation* It is well known that many conditions including surgical intervention may result in abolition of menstrual function either permanently or temporarily and it would therefore be reasonable to assume that operation on the ovaries might produce this change

Among the 25 patients without cancer treated with ovarian lifting 19 menstruated normally afterwards although menstruation did not occur for a year in a few and for two years in one patient

With one exception the 6 patients in whom menstruation did not return were over 34 years of age while menstrual function was re established in 8 patients who were over this age

One patient became pregnant and aborted at the third month in the series from 1957—1958

The desirability of performing tubal resection at the time of ovarian lifting has been carefully considered but not as yet accepted One patient was asked to record the body temperature regularly and the chart distinctly showed the occurrence of ovulation since then the temperatures of all patients have been recorded

*Sexual function* One of the principal purposes of this study was to investigate if it was possible to preserve a normal sex life

Eighteen of the 25 patients without recurrence stated that their sexual

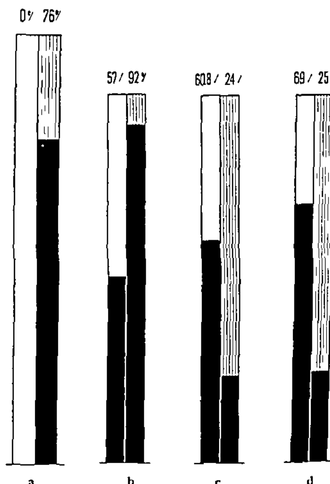



Fig 2 a) Frequency of preserved menstruation No patients with preserved menstruation after combined radium roentgen treatment in the control series (white column) Preserved menstruation in 76 of patients pretreated with ovarian lifting (black column) b) Frequency of unaltered or improved sexual function in the control series (black column left) and in patients pretreated with ovarian lifting (black column right) c) and d) Frequency of hot flushes (c) and of weight gain (d) Control series (black columns left) and in patients pretreated with ovarian lifting (black columns right)

function was as normal as before the operation both as far as libido and frequency of intercourse were concerned Four others stated that dyspareunia had been present before the operation, and that no change had occurred, i e the conditions were unchanged in 22 out of 25 patients

One patient seemed to have derived benefit from the intervention in that her previous fear of becoming pregnant had disappeared Two patients, aged 37 and 38 reported that libido had disappeared after the treatment

Forty seven of the 70 patients of the control group were symptom free (frequency of recurrence 32 8 %) Information as to sexual function was available for 42 of these 47 patients Twenty four stated that no change had occurred, 4 had ceased to have sexual relations for fear of recurrence 11 reported a definite deterioration, and 3 could give no worthwhile information

*Depth and degree of moisture of the vagina* The significance of measuring the depth of the vagina was unfortunately not appreciated at the beginning of the investigation but the vaginal depth was measured after treatment in two groups in which ovarian lifting or castration had been performed In none of the patients in the first group did vaginal shortening amount to more than 50 %

The depth of the vagina in patients undergoing ovarian lifting or castration was as follows

| | Average | Maximum | Minimum |
|---|---|---|---|
| After ovarian lifting | 10 cm | 12 cm | 6 cm |
| After castration | 7 » | 10 » | 1 » |

The vaginal mucosa was normal being moist non atrophic and folded i e unaffected by the treatment in the 19 patients with preserved ovarian function

The vaginal mucosa was studied in 40 of the patients in whom castration had been performed It was dry and atrophic in more than 60 % and dry and agglutinated in 10 % of these patients

*Weight gain* Weight gains were smaller in the patients who had undergone ovarian lifting than in those subjected to combined radium and roentgen irradiation (castration) Among the 42 patients treated with radium and roentgen irradiation in whom menstruation failed to reappear definite weight gains were observed in 29 (or 70 %) including 5 in whom the gains exceeded 5 kg

Weight gains were observed in 25 % of the patients treated with ovarian lifting but did not exceed 5 kg in any of the patients The fatty tissue increase was especially marked on the abdomen and thighs

*Postmenopausal symptoms* Six (or 24 %) of the patients who had had ovarian lifting complained of hot flushes while 19 had no postmenopausal symptoms Flushes occurred in 32 (or 76 %) of the 42 patients in the control series i e they were three times as frequent as after ovarian lifting

It may be mentioned with regard to complications that two patients of the entire series (1949—1950 and 1957—1958) had to be subjected to a second operation for unilateral ovarian cysts

## Conclusions

Ovarian function was preserved in 25 out of 32 patients aged from 23 to 39 of the entire series with carcinoma of the cervix uteri after lifting of the ovaries

from the field of irradiation and their fixation at a higher level The possibility of preserving ovarian function, an intact vagina, and normal tonus of the breasts as well as ensuring a normal sex life with this type of operation must constitute an important factor from the aspect of the welfare and happiness of the patient

Two (one from 1949 and one from 1957) of the 42 patients became pregnant and aborted at the third month It must consequently be assumed that the chances of a successful termination of pregnancy are poor

## SUMMARY

Attempts were made to preserve the ovarian function in young women with cervical carcinoma stage I by lifting the ovaries and attaching them to the parietal peritoneum on the psoas muscle or retroperitoneally to this muscle before radium irradiation The attempts proved successful in 25 of 32 patients aged from 23 to 39 The possibility of a normal sex life was considerably increased

## ZUSAMMENFASSUNG

In Fällen von Cervixcarcinom im Stadium I wurde versucht die ovarielle Funktion zu behalten indem man die Ovarien heraufzog und sie am parietalen Peritoneum des Psoas oder retro-peritoneal hinter diesem Muskel befestigte bevor Bestrahlung stattfand Diese Versuche bewährten sich gut in 25 von 32 Patientinnen im Alter von 23 bis 39 Jahren Die Möglichkeit eines normalen Geschlechtslebens war erheblich verbessert

## RÉSUMÉ

Les auteurs ont essayé de préserver la fonction ovarienne de jeunes femmes atteintes de cancer du col au stade I en fixant leurs ovaires en position haute au péritoine pariétal du psoas ou sous le péritoine a ce muscle avant curiethérapie Ces essais ont été suivis de succes chez 25 femmes sur 32 agées de 23 à 39 ans La possibilité d une vie sexuelle normale a été considerablement augmentée

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FROM THE DEPARTMENTS OF RADIOLOGY AND MEDICINE UNIVERSITY OF ARKANSAS MEDICAL CENTER AND THE RADIOISOTOPE SERVICE, VA HOSPITAL, LITTLE ROCK ARKANSAS U S A

# EFFECTS OF ROENTGENRAYS ON THE ENZYME SUBSTRATE (LUCIFERASE-LUCIFERIN) SYSTEM OF THE CRUSTACEAN CYPRIDINA

by

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Both the site of the primary cellular lesion and the earliest physiological changes produced in animals by ionizing radiation have been investigated for several years Most of the recent studies deal with alterations in the membrane permeability of certain intracellular structures (KAPLAN 1955) The increase in the activity of several enzyme systems observed after irradiation may be due to changes in membrane permeability BACQ & ALEXANDER (1961) have postulated that enzymes are released from membranes and intracellular surfaces by radiation Physiological changes then would be produced by the liberated enzymes DNA however is very radiosensitive while DNAase cannot be liberated by small doses of radiation (OKADA et coll 1957)

Other possible explanations for the increase in enzyme activity observed after irradiation might be (1) a substrate is rendered more susceptible to enzyme action or (2) substrates are partly destroyed leaving unused enzymes to accumulate

To obtain some information about the relative radiosensitivities of an enzyme and its substrate we have done in vitro studies on the effect of radiation on the

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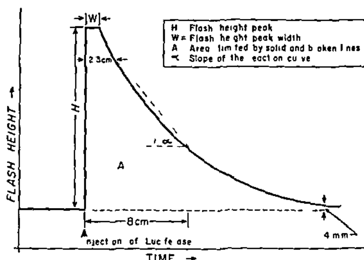



Fig 1 Schematic figure for explaining the abbreviations used in text and figures

enzyme substrate (luciferase luciferin) system of the small ostracod Cypridina This system is an excellent one because both the enzyme and the substrate are in highly purified states and can be irradiated separately

*Material and Methods* In these experiments an RCA type 6217 phototube with a range of highest response from 3 500 to 6 000 Å and a Moseley X Y chart recorder were used The negative voltage to the phototube was obtained from a Baird atomic model 312A super stable high voltage supply The phototube as well as a test tube with fixed geometry relative to the phototube were in a light tight box

All irradiations were done with a beryllium window roentgen tube (Philips Electronics Instruments Mt Vernon, N Y ) operated at 100 kV and 12 mA and producing a dose rate of $9 \times 10^4$ r/min

Four hundred micrograms of highly purified luciferin were dissolved in 4 ml of methyl alcohol In this solution pure luciferin is relatively stable The luciferase solution consisted of 400 μg of enzyme dissolved in 4 ml of 0 1 M phosphate buffer Twenty five lambda samples of the luciferase solution were pipetted into a small lucite container and irradiated with different doses of roentgen rays (3 000 to $4.5 \times 10^6$ r)

After irradiation, the sample was diluted to 10 ml with 0 1 M phosphate buffer at pH 7 0 making a final concentration of 0 25 μg/ml Also 25 λ of the methanolic luciferin solution were diluted to 10 ml with 0 1 M phosphate buffer producing a final concentration of 0 25 μg luciferin/ml

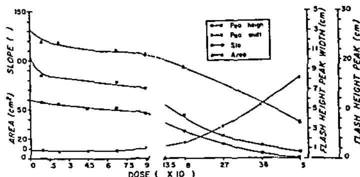



Fig 2 Flash height peak area slope and peak width of the *Cypridina* luciferase luciferin system as a function of the roentgen dose given to luciferase

First 10 ml of the buffered luciferin solution were poured into the test tube inside the light tight box The reaction was then initiated by injecting rapidly with a hypodermic syringe, 10 ml of the 0 25 $\mu$g/ml buffered, irradiated luciferase solution

To demonstrate the effect of the radiation on luciferin 25 λ of the 0 1 mg/ml methanolic luciferin solution were irradiated under the same conditions as the luciferase After diluting to 10 ml with 0 1 M phosphate buffer the solution was poured into the test tube and mixed with unirradiated luciferase solution (10 ml) using the method mentioned above The total light emitted (area under the curve), the slope of the reaction curve the flash height peak and the flash height peak width as illustrated in Fig 1 were determined immediately after mixing the enzyme and the substrate

Unirradiated control samples were used with each particular experiment Autoxidation could not be observed during the time measurements were made All measurements were made at room temperature

## Results and Discussion

The distribution of the values of flash height peak area slope and peak width for luciferase as a function of the roentgen dose is shown in Fig 2 Each individual point represents the mean of several experiments As can be seen the enzyme is very radioresistant There is only a slight change in the activity for doses up to about $10^5$ r For higher doses the peak height and the slope decrease simultaneously The area however decreases at a much slower rate The total light emitted is reduced by only about 50 % after irradiation with 3 6 × $10^5$ r This is probably not due to an influence of the concentration of the enzyme as will be shown later on Related to this might be an increase in the peak width of about 800 % after irradiation with 3 6 × 10 r

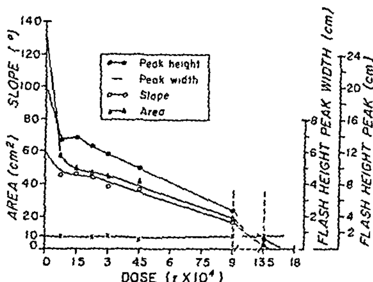



Fig. 3. Flash height peak, area, slope, and peak width of the *Cypridina* luciferase-luciferin system as a function of the roentgen dose given to luciferin

The results obtained by the irradiation of luciferin are shown in Fig. 3. In this case the area, the slope, and the peak height decrease almost at a constant rate within experimental error, but the peak width remains constant. A dose of about 13.5 × 10⁴ r destroys almost completely the substrate.

In Figs 4 and 5 the flash height peaks and the areas, as obtained after the irradiation of luciferase and luciferin, are compared. The curves were normalized to the control values. As can be seen, the enzyme is much more radioresistant than the substrate.

To demonstrate the effect of the concentration of either enzyme or substrate on the peak height, the slope and the area, different amounts (5 to 40 λ) of unirradiated luciferase or luciferin solution were mixed together in the test tube. The results are shown in Fig. 6. The peak heights decrease proportionally with decreasing total amounts of either enzyme or substrate. The experimental results are fitted by a straight line and can be represented by the equation $y = 1.17x$. By using half the initial amount (20 λ) only, the peak height is reduced by half. A straight line could also be obtained for the area in case of adding different amounts of luciferin to 40 λ of luciferase. There was, however, no linear decrease in the area with decreasing volumes of luciferase and a constant amount of luciferin (40 λ). A reduction of about 50 % in the amount of the enzyme changed only slightly the total light emitted. The observation can account for the effect mentioned earlier and shown in Fig. 2. Irradiation of luciferase required 3.6 × 10⁵ r to reduce the total light emitted by 50 %. The

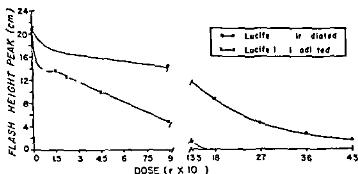



Fig 4 Flash height peaks of the *Cypridina* luciferase luciferin system as a function of the roentgen dose

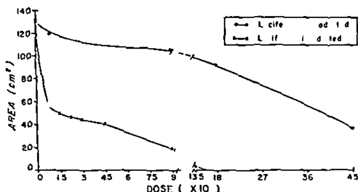



Fig 5 Area (totally emitted light) of the *Cypridina* luciferase luciferin system as a function of the roentgen dose

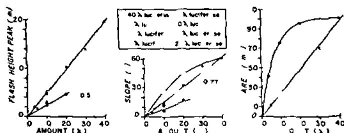



Fig 6 Flash height peak area and slope of the *Cypridina* luciferase luciferin system as a function of the quantity of each constituent

decrease in total light emitted is not proportional to a decrease in enzyme concentration However the decrease in the flash height peak is proportional to the reduction in enzyme concentration and can be used as a measure of radiation effect on the enzyme

The substrate, luciferin, appears to be more radiosensitive than the enzyme, luciferase A 50 % reduction in the total light emitted is produced by less than $1 \times 10^4$ r when given to luciferin However, the same amount of reduction in total light emitted produced by irradiation of luciferase requires about $30 \times 10^4$ r

A reduction in luciferase concentration of about 75 % as measured by total light output, is required to decrease total light output by 25 % using non irradiated samples Thus, a large amount of luciferase would have to be destroyed by irradiation before significant loss of activity could be found, using the area determination

The flash height peak is a linear function of the quantity of luciferase present If the flash height peaks are used as criteria for radiosensitivity, luciferase is 3 to 4 times more radioresistant than luciferin, as determined by the 50 % reduction in flash height peaks of the reaction curves

## Acknowledgements

We appreciate the generosity of Drs F H Johnson and Shimoura (Princeton University) in furnishing us with luciferin and luciferase and for their valuable advice The technical assistance of Mike Ebert and Miss Luanne Strickland is gratefully acknowledged

## SUMMARY

Twenty five lambda of practically pure luciferase solution (0 1 mg/ml of 0 1 M phosphate buffer) or 25 λ of highly purified luciferin solution (0 1 mg/ml of methyl alcohol were irradiated with different doses of roentgen rays (3 000 to $4.5 \times 10^5$ r) The initial flash height peak the slope of the reaction curve and the quantity of light emitted after combination of enzyme and substrate were determined using photocell equipment The results of these in vitro experiments show that the substrate is much more radiosensitive than the enzym

## ZUSAMMENFASSUNG

Funfundzwanzig lambda von praktisch reiner Luciferase Losung (0 1 mg ml einer 0 1 M Phosphatpuffer Lösung) oder 25 λ einer hochgereinigten Luciferin Lösung (0 1 mg ml Methyl alkohol) wurden mit verschiedenen Röntgendosen bestrahlt (3 000 bis $4.5 \times 10^5$ r) Das anfängliche Maximum der Abfall der Reaktionskurve und die nach Kombination von Enzym und Substrat freiwerdende Lichtmenge wurden mittels einer Photozelle bestimmt Die Ergebnisse dieser Versuche in vitro zeigen dass das Substrat wesentlich strahlenempfindlicher als das Enzym ist

## RÉSUMÉ

Vingt-cinq lambda d une solution pratiquement pure de luciférase (0 1 mg ml de 0 1 M phosphate tampon) ou 25 lambda de solution de luciférine très purifiée (0 1 mg/ml d alcool méthylique) ont été irradiés par différentes doses de rayons roentgen (3 000 à $4.5 \times 10^5$ r La hauteur de l éclair initial la pente de la courbe de réaction et la quantité de lumiere émise après la combinaison de l enzyme avec le substrat ont été measurées avec un équipment à cellule photo-électrique Les résultats de ces expériences in vitro montrent que le substrat est beaucoup plus radiosensible que l enzyme

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# SEMI-PORTABLE WHOLE BODY COUNTER FOR CESIUM 137 AND OTHER GAMMA EMITTING ISOTOPES

by

Y NAVERSTEN R C McCALL and K LIDÉN

After the discovery of the unusually high $^{137}$Cs burdens in Swedish Lapps (LIDÉN 1961) it was realized that a large group of people had to be studied to assess the actually existing contamination levels Since the people to be measured were about 1 700 kilometers from the iron room whole body counting facility (IRC) at Lund and since the Lapps are not easily available for long distance travelling it was decided to design and construct a whole body counter suitable for transport to Lapland

The whole body counter was designed around the following specifications

1 It should be semi portable i e two men should be able to assemble or disassemble it for transport in a few hours

2 It should have the same geometry as the 42 cm chair arrangement in the stationary whole body counter at Lund (CEDERQUIST & LIDÉN 1962)

3 The detector should be a 5 in diam by 4 thick NaI(Tl) crystal

4 Shielding must be presently available material i e lead bricks, the amount of shielding must be minimized to facilitate transport

5 It must be structurally safe

It was expected that the Lapps would have $^{137}$Cs body burdens in the range of 0 1 $\mu$C $^{137}$Cs or more With such a relatively large amount of activity it was not necessary to have a very low background We were also of the opinion that

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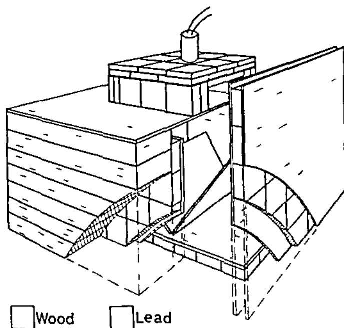



Fig 1 Semi portable whole body counter The shielding is supported by a structure of 8 × 4 timbers and plywood sheets

determination of the body content of potassium was of a second order of importance

There was very little experience to draw upon in the literature ROESCH et coll 1961 PALMER 1962 and LINDELL 1962 have done some work with simple shields

*Description of the whole body counter* A stable basic structure of 8 × 4 timbers is made with a plywood roof (Fig 1) A lead floor 4 cm thick is then laid The wooden structure is used to support side walls of lead 4 cm thick with an inner retaining wall of plywood A section of the pl[illegible] is cut out and replaced by a 4 mm lucite sheet in the area where [illegible] the subject must pass to reach the detector The detector 5 inch [illegible] in diameter and 4 inches thick NaI(Tl) crystal rests upon this sheet of lucite A small house of lead the walls and roof of which are 8 cm thick is built around three sides and above the top of the crystal The fourth side must be open in order to let the γ rays pass from the head and shoulders of the subject to the crystal In order to strengthen the ply[illegible]d roof a 30 mm by 30 mm by 5 mm right angle iron beam is added at the head end of the plywood roof A lead wall 4 cm thick held in position [illegible] two sheets of plywood is built immediately behind the subject to close th[illegible]

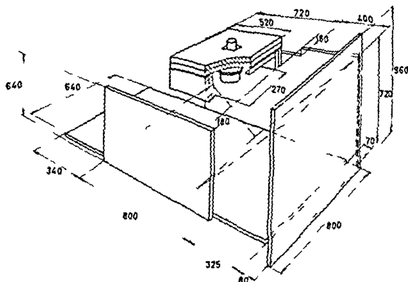



Fig 2 Arrangement of the lead shielding of the semi portable whole body counter The position of the chair is indicated by dashed-dotted lines

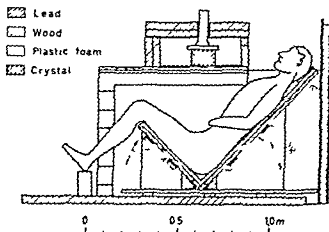



Fig 3 Profile view showing the geometry of the semi portable whole body counter The principle of the folding chair is indicated by arrows and dashed lines The lead shield of the side walls of the counter is not shown The crystal rests on a lucite sheet replacing the plywood area inside the lead cave

The arrangement of the lead shielding of the semiportable whole body counter (PC) is shown in Fig 2 The weight of the shield is about 1 200 kg The total weight of 1 500 kg is small enough that most floors can easily stand the counter without further support



Fig 4 The semi portable whole body counter seen from two different directions with a child in measuring position The bags containing 5 kg of sugar are used for background measurements

It was decided to avoid using a door since this would greatly increase the complexity of construction The outer dimensions of the counter thus constructed are only 160 cm (length) by 120 cm (width) by 110 cm (height) This small size was made possible by using a folding chair of plywood sheets (Fig 3) The subject walks into the shield and sits down on the chair, which is folded flat on the floor The chair is then erected to the standard chair position until the subject sits comfortably in a well defined geometry Since the head of the subject protrudes out of the shield (Figs 3 and 4) there is no problem of claustrophobia

*Factors influencing the background* Background studies made at our laboratory showed that additional lead would decrease the background only slowly in comparison to the amount of shielding needed We have estimated the unshielded openings in different directions according to Table 1 to be about 20 % of full solid angle $4\pi$ The measured reduction of the total background counting rate was also about 80 %

Of those openings mentioned in Table 1 (see also Fig 2) only the first one by closing it could reduce the background to the expense of a reasonably small amount of lead Measurements at our laboratory showed that a lead shield, 4 cm thick above the stem of the photomultiplier could reduce the background of the $^{137}$Cs energy band (0 60 to 0 72 MeV) and the potassium energy band (1 38 to 1 56 MeV) with 5 and 10 % respectively

The improvement by adding a lead wall 4 cm thick at the foot end of the counter was also investigated A wall 64 cm wide and 48 cm high suppressed the background of the $^{137}$Cs energy band by about 7 % and the background of the potassium energy band by about 6 %

**Table 1**

*Location of unshielded parts of the counter and their size in per cent of the full solid angle 4 π (as seen from the crystal)*

| | % |
|---|---|
| The opening for the stem of the photomultiplier above crystal | 3 |
| The entrance of the counter | 3 |
| The upper part of the side walls | 4 |
| The foot end of the counter | 6 |
| The head end of the counter | 3 |
| All openings | 19 |

**Table 2**

*Background of the semi portable whole body counter on different locations*

| Location | cpm in the energy bands | | Background ratio (II/I) |
|---|---|---|---|
| | I<br>600 to<br>720 keV | II<br>1 380 to<br>1 560 keV | |
| No 1 | 280 | 230 | 0.82 |
| » 2 | 650 | 530 | 0.82 |
| » 3 | 410 | 330 | 0.80 |
| » 4 | 180 | 120 | 0.67 |
| » 5 | 29 | 13 | 0.45 |

*Place No 1 Lund* (55.7 N, 14.6 E), Sweden. The counter in the middle of an air conditioned room, room dimensions about 10 × 5 × 2 m³, floor about 2 m below ground level, concrete walls, ceiling and floor.

*Place No 2 Jokkmokk* (66.6 N, 19.9 E), Sweden. The counter in the middle of a room of the following approximate dimensions 4 × 3 × 2 m³, floor about 2 m below ground level, concrete walls, ceiling and floor.

*Place No 3 Jokkmokk* (66.6 N, 19.9 E), Sweden. The counter in the middle of a room close to that of place No 2, room dimensions about 6 × 6 × 2 m³, floor about 2 m below ground level, concrete walls, ceiling and floor.

*Place No 4 Inari* (68.9 N, 27.0 E), Finland. The counter in the middle of a room in a wooden house, room dimensions about 5 × 5 × 3 m³, floor about one meter above ground level.

*Place No 5 Lund* (55.7 N, 14.6 E), Sweden. The detector in an air conditioned iron room 210 cm by 250 cm by 195 cm (height), walls and floor 18 cm thick of laminated iron, the ceiling shield consists of 1 cm iron and 8 to 12 cm lead, the floor about 2 m below ground level.

In such a counter with only moderate shielding the background is very dependent on the environmental radiation. It was expected that our measurements in the laboratory room with concrete walls, ceiling and floor, the floor being about 2 m below ground level, would in some respects constitute an un

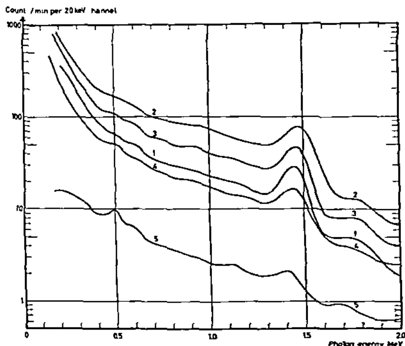



Fig 5 Background spectra in the energy range from 0.2 to 2.0 MeV obtained in the semi portable whole body counter at the four places mentioned in Table 2 compared with the background in a conventional iron room (spectrum No 5) The dominant peak is mostly from potassium in the environment of the counter Small amounts of radon daughters can be distinguished from various bumps

favourable background situation The background should be significantly lower in a wooden house and in a room above ground level

The backgrounds in Table 2 are measured with a 70 kg non radioactive sugar phantom in the counting position it can be seen that the background of the PC could vary within wide limits probably almost exclusively depending on the degree of radioactive contamination in the neighbourhood of the counter The relation between the counting rate of the $^{137}$Cs energy band and that of the potassium energy band shows that there is a qualitative difference between the various background spectra The concrete is undoubtedly contaminated with radionuclides emitting high energy gamma rays

Background spectra as they are obtained at places mentioned in Table 2 are shown in Fig 5 For comparison a background from the IRC is shown too (curve No 5) Backgrounds at places Nos 2 and 3 are definitely elevated probably due to a higher contamination level of natural radioactivity in the surroundings The peaks and bumps can be interpreted as gamma rays from dis

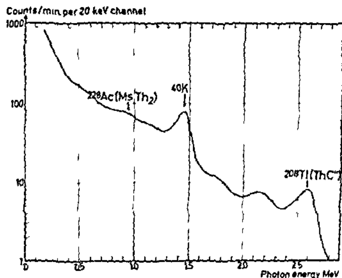



*Fig. 6. Background spectrum obtained in the semi-portable whole-body counter at place No. 2. The marked peak at 2.62 MeV and the bump at 0.96 MeV from thorium daughter products to some extent explain the relatively high background at this place.*

integrating nuclides of the uranium and thorium series and of $^{40}$K. In Fig. 6 is shown the background from place No. 2 in the energy range from 0.2 MeV to 2.9 MeV. Besides the peaks and bumps noticed in Fig. 5, a peak at 2.62 MeV from $^{208}$Tl of the thorium series is visible. The most predominant peak at 1.46 MeV originates from naturally occurring $^{40}$K in the neighbourhood of the detector.

To be able to make accurate whole-body radioactivity determinations it is also important to take into account the effect on the background of varying body sizes. Owing to the moderate shielding, a sizable amount of background photons will be attenuated in a body placed in the counting position. Some of these will hit the crystal as degraded photons.

Photons which, in the case of empty chair, would not have hit the crystal will be directed towards the crystal by scattering processes in the body. Without passing at least 4 cm of lead, however, only those photons entering through the open foot end of the counter can hit the crystal at a scattering angle of less than 90°. Attenuation by the body of background $\gamma$-rays of a certain energy therefore will show up as a depression of the counting rate within its full energy peak. A smaller depression occurs in the energy range of its Compton distribution. Superimposed on this depressed background are then the counts from additional degraded photons scattering into the crystal by the object itself, most of them having an energy less than 511 keV.

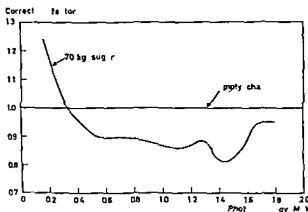



Fig 7 The effect on the background of photon interactions in a large mass in the counting position The background spectrum of a 70 kg sugar phantom is normalized to a background of empty chair

The effect on the background of varying body sizes has been studied with non radioactive sugar phantoms of several sizes in the counting position of the PC The phantoms were made in sections of 5 kg sugar bags They were built to resemble the shape of the body of a human being The ratio of the background of a 70 kg phantom to that of an empty chair, as a function of the energy is shown in Fig 7 The correlated spectra show the effect of photon interactions in large masses inside the counter Degraded photons will result in an elevated background counting rate of the channels below 300 keV Above 100 keV we obtained a markedly decreased background counting rate with a 70 kg sugar phantom in comparison to that obtained without sugar in the counter This is due to the attenuation in the phantom of photons penetrating the shield

The background in different energy ranges shows approximately a linear relation to the phantom mass in the region from 30 to 80 kg (Fig 8) The break of the lines of the high energy bands at about 30 kg could be a result of the attenuation of gamma rays from the floor outside the counter The first 30 kg sugar will obviously more effectively shield the detector from photons passing the lead floor than sugar does thereafter added to get larger phantoms Below 300 keV owing to scatter there is an increasing background counting rate with the phantom size The counting rate in the total energy range from 0 1 to 1 8 MeV also *increases with the phantom size* However, for all energy bands above 400 keV the counting rate decreases with phantom size

If a standard background is automatically or otherwise subtracted a further correction in order to get a correct net count is easily applied according to the following considerations

| | | |
|---|---|---|
| $N_{b\ St}$ | = standard background with a phantom weight of *St kg* | cpm |
| $N_{b\ X}$ | = background for a person with a weight of X kg | cpm |
| $f_{X\ St}$ | $= \frac{N_{b\ X}}{N_{b\ St}}$ = background correction factor | |
| $N_g$ | = gross count | cpm |
| $N_n$ | $= N_g - N_{b\ St}$ = net count before correction | cpm |
| $N$ | $= N_g - N_{b\ X}$ = true net count for a person weighing X kg | cpm |
| S | = sensitivity of the whole body counter | cpm/nc |

From these definitions the following formula is deduced

$$N = N_n + N_{b\ St}(1 - f_{X\ St}) \qquad \text{cpm (1)}$$

*The correction corresponds to a body burden of*

$$A_{corr} = \frac{N_{b\ St}}{S}(1 - f_{X\ St}) \qquad \text{nc (2)}$$

At place No 1 the change of the background in the $^{137}$Cs energy band due to different body sizes in the counter, was found to be 0 11 % per kg If a standard background with a 70 kg phantom is used and if the background is less than 700 cpm (see Table 2) this correction corresponds to less than *10 nc* $^{137}$Cs for a subject of 30 kg body weight

*Calibration of the semi-portable whole body counter for absolute measurements of* $^{137}$*Cs body burdens* The whole body counter was constructed to have the same geometry as the 42 cm chair arrangement of the stationary whole body counter at Lund (Cederquist & Lidén 1962) Therefore the calibration data of the latter in the first approximation should be applicable to the PC

However a small correction of the figure of sensitivity had to be made, since the detector in the PC was supported by a lucite sheet, 4 mm thick and the head end of the plywood roof of the counter had a 30 mm by 30 mm by 5 mm right angle iron beam By a somewhat simplified geometrical consideration it was calculated that the absorption of the $^{137}$Cs and $^{40}$K gamma rays amounted to 5 0 % and 3 4 %, respectively Therefore the counting efficiencies of those isotopes a priori were assumed to be correspondingly smaller in the PC than in the stationary facility Using the most recent level schemes of $^{137}$Cs and $^{40}$K (*Nuclear Data Sheets* 1959 and 1961) the sensitivity of the counter for these radionuclides at equilibrium in a subject of 70 kg body weight is 2 76 counts per minute per nanocurie $^{137}$*Cs and 0 180 counts per minute per gram potassium* The uncertainty of these figures is about 5 %

In order to test the counting efficiency of the PC great efforts have been made to compare it with result in the IRC Persons measured in places Nos 3 and 4 were transported by air and train to Lund to get comparable measurements as soon as possible However, it was not possible to arrange it without a delay

**Table 3**

*Comparable counting rates in the energy range from 0 60 to 0 72 MeV from $^{137}Cs$ as obtained with the same detector in the semi portable whole body counter and in the iron room whole body counter at Lund*

| Subject | Weight of the subject kg | Counting rate A in PC cpm | B in IRC cpm | Discrepancy (A—B) cpm | Significance of (A—B) 2 S D cpm |
|---|---|---|---|---|---|
| Y N | 72 | 185 | 177 | 8 | 8 |
| J C | 77 | 240 | 240 | 0 | 11 |
| Y N | 72 | 132 | 132 | 0 | 4 |
| E M | 61 | 900 | 903 | —3 | 34 |
| T M | 34 | 210 | 199 | 11 | 13 |

of a couple of days Table 3 shows the result of such measurements of different subjects in the PC and the IRC The counting rates of the PC have been corrected for 5 % absorption in the detector supporter All backgrounds used were obtained with non radioactive sugar phantoms of correct weight except for subject T M in the PC His background obtained with a 65 kg sugar phantom was corrected according to the formula (2) on page 191 using a relative background correction factor of 0 0011 All counting rates are also corrected for contribution of potassium counts in the $^{137}Cs$ energy band A correction is also made on the assumption of a daily excretion rate of 1 % Table 3 does not indicate any difference in the counting efficiency between the compared whole body counters

In the PC, children down to about 25 kg body weight were assumed to be measured Therefore it was desirable to take into account the relation between the counting efficiency and the body weight The iron room counter was calibrated for $^{137}Cs$ in the body for a standard man The efficiency variation with the body weight was not very particularly studied With a 7 in diam by 3 5 thick NaI crystal MILLER et coll (1959) have shown that the variation is less than 5 % of the sensitivity of potassium for a change in body weight from 50 to 96 kg With a 8 diam × 4 thick NaI crystal MILLER 1962 reported results indicating a variation of the sensitivity for potassium in the body of about 10 % for a change of 50 kg in body weight In our laboratory using a 5 × 4 NaI (Tl) crystal a decrease in the efficiency of about 10 %, for a change in body weight from 50 to 100 kg has been found

Measurements of cylindrical plastic containers filled with solutions of $^{137}CsCl$ have shown a rather wide variation of the counting efficiency for different parts of the body as could be expected from simple geometrical considerations (Fig 9) Each of the four sections consisting of two cylindrical plastic containers were counted while the other three were replaced by non radioactive sugar

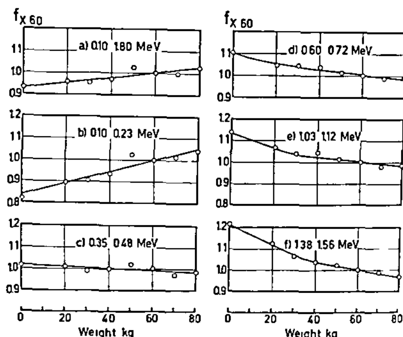



Fig 8 The background correction factor ($f_{X\,60}$) for different energy intervals obtained with several sizes of the sugar phantom Above 400 keV due to attenuation the background decreases with increasing mass In the low energy part of the spectrum due to additional degraded photons the background increases with the phantom mass

bags The figures indicate the relative counting efficiency They show that radioactivity in the lower parts of the legs is counted with a rather low efficiency By weighing the contribution to the counting efficiency of different parts of the phantom it was possible to get an idea of the variations with body weight below 50 kg The weight of the different counting efficiencies was obtained from a consideration of both the body size and the distribution of muscles within subjects with body weights of 25 and 50 kg respectively This calculation indicates a variation of the efficiency of 0 3 to 0 5 % per kg body weight from 25 to 50 kg the efficiency being higher for small body sizes

A direct measurement in the PC of a phantom of plastic cylinders containing $^{137}$Cs solution and resembling a subject of 20 to 25 kg body weight gave a sensitivity which was 19 % higher than that obtained with subjects of standard weight This corresponds to an average change of sensitivity of about 0 4 % per kg from 25 to 75 kg

From these considerations a variation of 0 3 to 0 5 % per kg from 20 to 50 kg and 0 2 to 0 3 % per kg from 50 to 100 kg body weight should be a rather good approximation

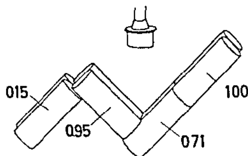



Fig 9 A simple synthesized phantom consisting of 4 compartments of double cylindrical containers The figures indicate the relative counting efficiency of the different compartments

Since this counter is constructed for measurements of relatively high body burdens of $^{137}$Cs, the contribution of potassium counts in the $^{137}$Cs energy band is of little importance These counts should never correspond to more than 4 nc $^{137}$Cs However, in most normal cases they correspond to about 1 nc $^{137}$Cs for subjects below 50 kg body weight for heavier persons about 2 nc $^{137}$Cs

The considerations above lead to the following general formula for determination of the body content ($A_{Cs}$) of $^{137}$Cs in human beings

$$A_{Cs} = \left[ \frac{cpm_C}{2\ 76\,[1 + 0\ 004\,(70 - w)]} - \begin{Bmatrix} 2, & w > 50\ kg \\ 1 & w \leq 50\ kg \end{Bmatrix} \right] nc\ ^{137}Cs \qquad (3)$$

where $cpm_C$ is the net counting rate in the interval of 0 60 to 0 72 MeV and w is the body weight of the subject

## Counting accuracy

The most important factor determining the accuracy in the evaluation of body burdens of radioactive isotopes is governed by the random occurrence of the pulses Table 4 shows the statistical accuracy of the determination of body burdens of $^{137}$Cs as indicated by one S D in per cent of the number of net counts The calculation is made on the assumption of counting times from 10 to 60 minutes for body burdens from 5 to 500 nc $^{137}$Cs and for three different background counting rates The first one corresponds to the relatively high background level at the place No 2 of Table 2 The second background represents a rather good counting situation for the PC at place No 4 of Table 2 For comparison the statistical accuracy of the IRC at Lund is calculated where the background counting rate is about 30 cpm in the same energy band In all cases the sensitivity is assumed to be 2 76 cpm/nc From Table 4 it is calculated that the greatest standard deviation for a 10 minute gross count and a 10 minute background count corresponds to about 4 nc $^{137}$Cs independent of the body burden of this isotope If 2 S D is used as a measure of the statistical accuracy, the uncertainty owing to statistical fluctuations is less than 9 nc $^{137}$Cs

**Table 4**

*The statistical accuracy expressed as one S D in per cent of the number of net counts (the calculation is made for a sensitivity of 2 76 counts per minute per nanocurie of $^{137}Cs$ and for the same counting time and background)*

| Counting time min | Background cpm | Body burdens nc $^{137}Cs$ | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 20 | 50 | 100 | 200 | 500 |
| 10 | 650 | 83 | 42 | 21 | 8 | 5 | 2 | 1 |
| | 180 | 44 | 22 | 12 | 5 | 3 | 2 | 1 |
| | 30 | 20 | 11 | 6 | 3 | 2 | 1 | <1 |
| 20 | 650 | 59 | 30 | 15 | 6 | 3 | 2 | <1 |
| | 180 | 31 | 16 | 8 | 4 | 2 | 1 | <1 |
| | 30 | 14 | 8 | 4 | 2 | 1 | 1 | <1 |
| 60 | 650 | 34 | 17 | 9 | 3 | 2 | 1 | <1 |
| | 180 | 18 | 9 | 5 | 2 | 1 | <1 | <1 |
| | 30 | 8 | 4 | 3 | 1 | <1 | 1 | 0 4 |

The accuracy in the determination of body contents of $^{137}Cs$ is highly governed by the stability of the background which in most cases is a matter of holding the radon concentration at a constant level in the surroundings of the counter With fluctuating weather conditions the radon concentration is subject to considerable variation Since the radon daughter products especially RaC have several $\gamma$ ray lines above 0 6 MeV this varying radon concentration will effect the background counting rate in the $^{137}Cs$ energy band At the places Nos 2 and 4 the maximum deviation from the average of frequently measured 10 minute backgrounds of the $^{137}Cs$ energy band was about 2 S D This variation was too small to be significantly attributed to a varying radon concentration Therefore with very simple precautions the uncertainty owing to this variation probably should correspond to less than 2 nc $^{137}Cs$

The superficial radon contamination of the subject itself is a problem of the same nature The only real cure is a shower for the subject especially his hair, and a change of clothes before measurements Without any precautions the superficial radon contamination could result in false counts in the $^{137}Cs$ energy band corresponding to several nc $^{137}Cs$ in excess of the real body content

The background depression owing to the subject in the counter also could give an error if the background phantom in its scattering properties does not sufficiently well resemble the subject The magnitude depends on the background level In our case this error should not correspond to more than 2 nc $^{137}Cs$

The correction for potassium counts distributed in the $^{137}Cs$ energy band is certainly assessed within 1 nc $^{137}Cs$

Summed up, a carefully evaluated value of a subject's body burden of $^{137}$Cs from a 10 minute measurement in the PC should not be in error by more than 15 nc $^{137}$Cs

It is the opinion of the authors that this simple counter could find applications for medical and other survey purposes, in many cases offering a good alternative to the more complex and expensive whole body counters of the iron room type


## Acknowledgements

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One of us R G McCall was supported by a Research Fellowship from the National Cancer Institute Public Health Service U S A


### Addendum in the proofs

Recently (in March and April 1963) the counter was used as a mobile unit in a big motor bus The counter was placed in the middle of the bus The floor of the counter was about 80 cm above ground level The mobile unit was used at a distance of less than 20 m from the rooms defined as place No 2 and place No 3 in Table 2 The backgrounds of the energy bands I and II were then 150 cpm and 85 cpm respectively The background ratio (II/I) was 0 57 At 8 different places along more than a 2 000 km long road from northern to southern Sweden the background of band I varied from 110 cpm to 230 cpm The background of band II varied from 65 cpm to 130 cpm and the background ratio from 0 48 to 0 73


## SUMMARY

A whole body counter for determination of body burdens of $^{137}$Cs and other isotopes is described The counter easily assembled and disassembled has small dimensions and the weight is less than 1 500 kg The background reduction is obtained by lead shielding The effect on the background of the radioactive environment and of the size of the subject has been studied The measuring geometry a 5 × 4 NaI(Tl) crystal in a 42 cm chair geometry has been calibrated by comparison with a static iron room counter The sensitivity is 2 76 cpm/nc $^{137}$Cs The measuring accuracy as a function of body burden and background is analysed

## ZUSAMMENFASSUNG

Ein Ganzkorperzahler fur Best mm ng  M ngen on 137 Cs und anderen radioaktiven Isotopen im menschlichen Korper w rd  hri ben Der Zahler der leicht auf und abgebaut werden kann ist verhaltnismassig kl in u  legt w enig r als 1 500 kg Die Abhangigkeit des Nulleffekts von der radioaktiv n Kont amin erung d r Umgebung und von der Korper grosse sind studiert worden Der Gan korperzahler e  Natriumjodidkristall (12 5 cm × 10 cm) in 42 cm Stuhlgeometrie  t mit Hilfe von Vergleichsmessungen mit einem statio-

naren Stahlkammerzahler kalibriert worden Die Empfindlichkeit wurde als 2 76 Imp/min pro nc 137 Cs festgestellt Die Abhangigkeit der Messgenauigkeit von der Körperaktivitat und von der Grosse des Nulleffekts wird analysiert

## RÉSUMÉ

Les auteurs décrivent un compteur humain total pour la mesure de la charge du corps humain en 137 Cs et en autres isotopes Ce compteur facilement monté et démonté est de petites dimensions et pèse moins de 1 500 kg La réduction du bruit de fond est obtenue par un blindage de plomb L effet de la radioactivité ambiante et des dimensions du sujet sur le bruit de fond a été étudié La geometrie du dispositif de mesure un cristal de NaI (Tl) de 5 × 4 pouces distant de 42 cm du fauteuil a été étalonnée par comparaison avec un compteur fixe dans une chambre blindée de fer Sa sensibilité est de 2 76 cpm/nc 137 Cs L exactitude de la mesure en fonction de la charge du corps humain et du bruit de fond a été étudiée

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# DEVELOPMENT OF THE SWEDISH ROENTGEN STANDARD LABORATORY EQUIPMENT

by

R THORAEUS

The free air standard chamber is still the primary instrument for the experimental realization of the international roentgen at radiation energies up to 500 kV Fully aware of the fundamental importance of having access to such a chamber standard laboratories and many radiotherapy centres have designed and installed such units In Sweden a complete standard laboratory for measurements of roentgen radiation excited by tube voltages up to 200 kV constant potential was planned and designed in 1929 In 1930 the installation was in operation at our institute (ref 4) and the free air standard chamber then installed is still used as the national standard Improvements of details have naturally been introduced since then but always in such a way that continuity is maintained Some of the improvements will now be described

An increase of the calibration capacity of the standard laboratory above 200 kV was planned by the author at the beginning of the nineteen fifties With monetary grants from the Government and from the Anti Cancer Society of Stockholm it was possible to order and install an encapsulated high voltage generator capable of 300 kV constant potential, designed to specified qualifications and a 300 kV roentgen tube of special design capable of operating from 6 to 300 kV constant potential with 25 mA at 10 kV and

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4 mA at 300 kV A photograph of this tube is shown in Fig 1 The electrostatic high tension voltmeter mentioned below is seen to the left and the new generator to the right The installation was completed in July 1954 and is still in use

Three different types of instrumentation were at our disposal for measurement of the constant potential tube voltage

1 A sphere gap with spheres of 30 cm diameter, capable of voltage measurements up to 350 kV

2 An electrostatic voltmeter of the Abraham Villard type, this can be used from 6 to about 250 kV by overlapping ranges

3 Two high ohmic oil immersed resistor units in the high voltage generator tanks The current through these units is measured by a microammeter positioned in the switch table and provided with a scale showing the tube voltage in kV This instrument has two sensitivity ranges 0 to 100 kV, and 0 to 300 kV which can be used alternatively

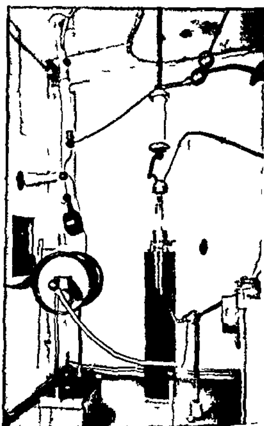


Fig 1 The 300 kV roentgen tube in the standard laboratory To the left the electrostatic voltmeter measuring the tube voltage

At the end of 1954, low voltage d c high ohmic resistor units were constructed, they were produced by adding a large number of 5 megohm resistors The resistance of each of them was determined by measurements using a voltmeter and a microammeter, both calibrated with an accuracy of ± 0 2 per cent, and battery potentials of 250 to 400 volt Some of the resistors were tested with ten to fifteen different potentials between 40 and 700 volt showing close proportionality between potential and current and thus a satisfactory constancy of the resistance

The 5 megohm resistors used are tube shaped and can therefore easily be mounted on a perspex rod In this way two reference resistor units of accurately known resistance were constructed each about 1 metre in length Their resistances are 95 74 and 95 60 megohm respectively They can be used single in parallel, or in series When not used the units are stored in closed tubes of laminated paper thus effectively protected from dust and easily handled

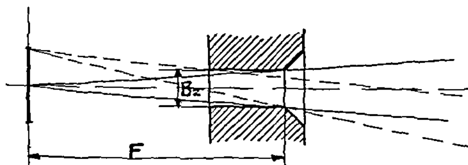



Fig 2 Distortion of beam and plane of definition if the focal size projection on a focal plane perpendicular to the centre line of the beam is greater than the diaphragm diameter

The resistance of each individual resistor of the units can be re checked whenever wanted

The resistance of the two oil immersed high ohmic resistors mentioned above was then determined by current measurements, using battery potentials between 5 000 and 10 000 volt measured by the reference resistor units and a microammeter The high ohmic resistors are commercially available and nominally of the order of 500 megohm Another set of two such calibrated oil immersed resistors and a microammeter in the switch table are used for measurement of the constant potential tube voltage obtained from a separate high voltage generator used in operating different types of roentgen tubes for short focal distance therapy

In a personal communication Dr H O Wyckoff of the NBS Washington has informed the author of a recent paper from the Bureau (ref 2), describing a new design for an accurate d c standard resistor similarly made up of a large number of resistors connected in series but arranged to form a vertical helix in air between a ground plate and a high voltage electrode This resistor unit is designed for direct measurements of high voltages

For various reasons the roentgen tube of a free air standard chamber installation should have the smallest possible focus size and emit the smallest possible percentage amount of off focus radiation (ref 5) A special reason for using a small focus is illustrated in Fig 2 As may be seen the plane of definition of the diaphragm becomes undefined if the focus size is greater than the diameter of the diaphragm aperture

The 300 kV roentgen tube in Fig 1 has the focus characteristics indicated by the natural size pinhole photographs in Fig 3 The normally exposed photograph (Fig 3a) shows that the size of the focus spot is about 5 × 6 mm The photograph in Fig 3b 10 times longer exposed reveals an overexposed focus spot and a small amount of off focus radiation Both photographs were taken at a tube voltage of 150 kV constant potential without additional filter The tube wall window (inherent filtration) is of 3 mm thick beryllium

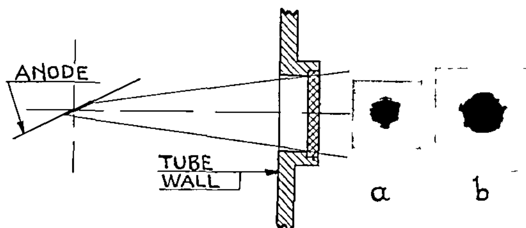



Fig 3 Section through the roentgen tube of the free air standard chamber equipment and natural size pinhole photographs of the focal region

One roentgen of the radiation used produces in a free air chamber a corpuscular emission such that when an arbitrary measuring volume of free, i e unrestricted, air at standard atmospheric conditions is irradiated, saturation current and electronic equilibrium conditions prevailing, and the maximum range of the corpuscles being fully utilized, ions carrying one electrostatic unit of quantity of electricity are obtained per cubic centimetre of the irradiated measuring air volume In the experimental realization of the unit the quantity of electricity collected may readily be measured by a suitable instrumental equipment compared to which the measuring air volume used is usually a number of cubic centimetres, which has to be determined by calculation

The ionization current measuring system of a free air chamber forms an electric circuit, the stability of which may easily be checked A constant source of ionization current is then substituted for the ionization in the chamber and the change in potential in the collecting precision capacitor is measured as usual The ionization current most convenient for this purpose is obtained by using the corpuscular emission (alphas or betas) from a radioactive substance of long half life A uranium ionization current standard has for a long time been used in our standard laboratory with good result

One of our collecting capacitors consists of coaxial brass tubes with air as dielectric medium, except at the ends where the tubes are mechanically fixed in position by small amber rings This capacitor is protected against stray radiation by 3 mm lead + 1 mm brass It was separately calibrated at three standard laboratories abroad (ref 9) The values obtained were as follows

| | |
|---|---|
| In England (1953) | 201 4 μμF |
| In Germany (1954) | 201 2 μμF |
| In U S A (1956) | 201 2 μμF |

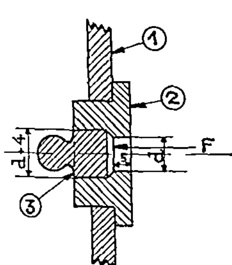



Fig 4 Section through earlier beam-defining diaphragm arrangement 1) Front wall of standard chamber 2) interchangeable diaphragms of different aperture d 3) beam absorbing plug

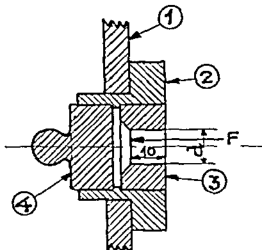



Fig 5 Section through the new beam-defining diaphragm arrangement 1) Front wall of standard chamber 2) diaphragm holder 3) interchangeable diaphragms of different aperture d 4) beam absorbing plug

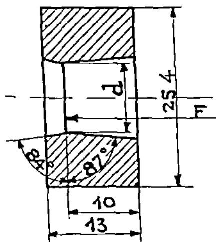



Fig 6 Diaphragm disc in which a lightly coned surface replaces the cylindrical surface

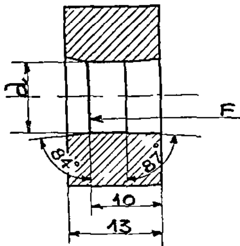



Fig 7 Diaphragm disc in which a slightly coned surface replaces part of the cylindrical surface

It appears that the values are very nearly the same This shows that the capacitor itself has the high constancy required for the purpose in hand

In 1956 when the portable Swedish free air standard chamber unit was calibrated at the NBS Washington the complete ionization current measuring equipments of the two free air units were directly compared one against the

other (ref 11) An agreement within 0 1 per cent was then found This is in accord with the last ICRU report (ref 1) in which a maximum error of ± 0 1 per cent is estimated for the charge measuring equipment

The measuring volume is defined by the length of the collector electrode and the geometry of the diaphragm system in relation to the roentgen tube and the collector electrode The length of the measuring volume is geometrically defined by the length of the collector electrode plus the sum of half the spaces between the collector electrode and the adjacent guard electrodes According to earlier experiments in this institute (ref 8) this method of defining the length has been found to hold true for lengths down to 1 5 cm using a space of 0 5 mm at each end of the collector electrode

The cross section of the measuring volume is defined by the diaphragm aperture and the beam geometry The diaphragm system used here, until the middle of the nineteen fifties, is shown in Fig 4 and consists of interchangeable diaphragms of different aperture diameters up to a maximum of 22 mm The beam defining part is a cylindrical hole 5 mm in length, this was considered sufficient to define the beam when tube voltages not above 200 kV constant potential were used The plane defining the cross section of the beam, and the direction of the radiation, are indicated by the arrow F in the figure This diaphragm system was described in detail in a previous paper (ref 7) It will only be mentioned therefore, that the material used was so called hard lead (90 per cent lead and 10 per cent antimony) and that the same system was used with the portable free air standard chamber unit, which was specially designed to be the intermediary medium in the comparison of the Swedish stationary standard chamber with those of Great Britain Western Germany, and USA (ref 8, 10, 11) and also was used to compare two of the foreign chambers (ref 11)

The use of a lead plug close behind the diaphragm aperture as shown in Fig 4 may be briefly explained This arrangement permits direct measurement of the total leakage correction without introducing modifications or changes of the scattering and other leakage conditions and their geometry It has been used in this standard laboratory for a long time at first in the stationary free air standard chamber and later also in the portable unit when this was used abroad in the period 1953 to 1956 (ref 11) It has been found to be both convenient and reliable The new modified diaphragm arrangement described below (see Fig 5) is particularly convenient as being so simplified that only one plug is required for all the diaphragms

In connection with the increase of the calibration capacity a modified diaphragm arrangement was introduced The cost of this was covered by a separate monetary grant from the Anti Cancer Society of Stockholm This system is shown in Fig 5 and consists of interchangeable diaphragm discs the aperture diameter of which can be up to a maximum of 22 mm, the beam defining part of the discs is a cylindrical hole 10 mm in length

**Table 1**

*Diameter of our diaphragm No. 8a*

| Diameter | Measurement results in mm | | |
|---|---|---|---|
| | Stockholm 1946 | Washington 1956 | Stockholm 1959 |
| Front | 8.005 | 7.99080 | 7.9920 |
| Middle | — | 7.99465 | — |
| Rear | (8.005) | 7.99719 | 7.9945 |

The material used for the whole system is a Swedish made heavy alloy of tungsten having a density of 18. This material has been found to be excellent for the purpose in question, and easy to machine. The diameter of the incident primary beam at the front surface of the diaphragm holder is always kept within the diameter of that surface (about 50 mm). The plane of definition, and the direction of the radiation are indicated by the arrow F.

The old and the new beam defining diaphragm arrangements may be used alternatively. This enables direct comparisons and thus a complete maintenance of the continuity. In addition the new diaphragm discs are given the same external dimensions as the diaphragm put at the disposal of standard laboratories by the NBS for comparison with their own diaphragms (ref. 1). A direct interchange for this purpose is thus very easy. Furthermore the disc shown in Fig. 5 has the same aperture form as the NBS diaphragm.

As has already been mentioned and illustrated in Fig. 2, a cylindrical diaphragm aperture can be used safely only if the size of the radiation emitting area projected on a plane perpendicular to the centre line of the beam is smaller than the aperture diameter. Therefore, when two diaphragms of different diameters are ionometrically compared errors may occur if one or both of the diameters are smaller than that of the radiation emitting area, or if the difference between them is great. It is however evident that this source of error may be eliminated if a slightly coned surface is used in place of the cylindrical surface. A diaphragm disc of this type is shown in Fig. 6. It appears that the angular thickness of the aperture edge at the plane of definition is 171 degrees. This is only 9 degrees less than the maximum available and much more than what is usually used (90 to 135 degrees). The correction required for the small amount of radiation transmitted at the top of the V shaped, circular edge constituting the plane of definition of the diaphragm is considerably reduced by this design.

A modification of the diaphragm in Fig. 6 is depicted in Fig. 7: here a slightly coned surface is used in place of part of the length of the cylindrical hole shown in Fig. 5.

The design using a coned surface in whole or in part, may be expected to give a more accurate position of the plane of definition. The high density of the material used further contributes to the improvement. The diaphragm

**Table 2**

*Results of ionometric measurements with different diaphragms in Washington 1956*

| Diaphragm No | Volt | Exposure time in seconds | Average volt per minute | Calculated relative values of ionization |
|---|---|---|---|---|
| 6a | 28 64<br>28 59<br>28 59 | 200 | 8 584 | 0 5636 |
| 8a | 25 37<br>25 38<br>25 36 | 100 | 15 22 | Average 15 23 = 1 000 |
| 8a | 25 40<br>25 38<br>25 42 | 100 | 15 24 | |
| 10a | 23 81<br>23 75<br>23 79 | 60 | 23 78 | 1 5614 |

**Table 3**

*Diaphragm diameters obtained from direct and ionometric measurements in Washington 1956 and from direct measurements in Stockholm 1959*

| Diaphragm No | Calculated from the relative values in Table 2 and the rear 8a value given in column 3 of Table 1 | Measured in Stockholm in 1959 | Difference (%) |
|---|---|---|---|
| 6a | 6 003 | 6 001 | 0 03 |
| 8a | 7 997 | 7 995 | 0 03 |
| 10a | 9 993 | 9 996 | 0 03 |

discs in Figs 5, 6 and 7 may be used alternatively, and a direct comparison is thus very easy

Our measurements in 1946 of diaphragm 8a, of the type shown in Fig 4 were made crosswise in two perpendicular directions at the front surface, a cylindrical hole being assumed from the method of machining In 1956 this diaphragm was separately measured with very high precision at the NBS and in 1959 was re measured at our institute by a measuring device more accurate than that used in 1946 All the results obtained with this diaphragm are collected in Table 1

The NBS results show that the hole is slightly coned with a calculated front rear average of 7 9940 ± 0 04 per cent This value is very nearly the same as that measured at the middle Our own values in the last column give a similar result The average is 7 9933 which is only 0 01 per cent different from the just mentioned average of the NBS values

Fig 4 shows that the rear diameter is that normally defining the cross section of the beam If we thus compare our latest rear value 7 9945 with that obtained at the NBS 7 99719 it appears that the difference is about 0 03 per cent

**Table 4**

*Measurement results obtained with each of the seven separate parts of the divided collector electrod*

| Collector electrode No | Length of collector electrode in cm | 165 kV HVL = 0 055 mm Cu V in volt per minute | 165 kV HVL = 0 35 mm Cu V in volt per minute |
|---|---|---|---|
| 1 | 5 00 | 11 21 | 11 54 |
| 2 | 5 00 | 11 20 | 11 58 |
| 3 | 5 00 | 11 15 | 11 53 |
| 4 | 5 00 | 11 05 | 11 50 |
| 5 | 5 00 | 10 86 | 11.54 |
| 6 | 5 00 | 10 84 | 11 52 |
| 7 | 5 00 | 10 85 | 11 50 |

As already mentioned, diaphragms of the type shown in Fig 4 were used as the intermediary medium in the comparison These diaphragms were ionometrically compared at the NBS free air standard chamber The results obtained are collected in Table 2

Diaphragms 6a and 10a have been re measured in our institute in the same way as shown above for diaphragm 8a The measurement results and the results calculated from the direct and relative measurements in Washington all of them to three decimals are given in Table 3 It appears that the difference is within ± 0 03 per cent

According to Rajewsky et coll (ref 3) it is usually possible to attain an accuracy of ± 0 003 mm in the measurement of the aperture diameter If the diameter is of the order of 10 mm the accuracy will be ± 0 03 per cent The differences in Table 3 agree with this

An error of ± 0 3 per cent is estimated in the last ICRU report (ref 1) in the determination of the measuring air volume The diameter error found above is only one tenth of that volume error As the maximum error that may occur in free air standard chamber measurements is ± 1 1 per cent (ref 1), further efforts to reduce the error in the determination of the diaphragm diameter will not appreciably influence the total accuracy

Two diaphragm discs have been produced to fit the new type of diaphragm holder shown in Fig 5 one of the type designated 3 in Fig 5 and one of the type shown in Fig 6 The first mentioned has a cylindrical hole 10 0165 mm in diameter and the other an aperture diameter of 10 0075 at the plane of definition

It is a common experience that a free air standard chamber equipment is mainly used for calibration of radiation measuring instruments provided with cavity ionization chambers or other detectors When such an instrument is to be calibrated in this laboratory its detector is arranged in the following way (ref 7) The detector is inserted into the beam through a special opening

**Table 5**

*Symmetrical addition of the experimental results in Table 4*

| Collector electrode No | l = total length of collector electrode in cm | 165 kV HVL = 0 055 Cu Sum of v | v/l | 165 kV HVL = 0 35 Cu Sum of v | v/l |
|---|---|---|---|---|---|
| 4 | 5 00 | 11 05 | 2 210 | 11 50 | 2 300 |
| 3+4+5 | 15 00 | 33 06 | 2 203 | 34 57 | 2 303 |
| 2+3+4+5+6 | 25 00 | 55 10 | 2 203 | 57 67 | 2 307 |
| 1+2+3+4+5+6+7 | 35 00 | 77 16 | 2 203 | 80 71 | 2 306 |
| | Average v/l | = | 2 205 | = | 2 304 |
| | | | ± 0 16 % | | ± 0 15 % |

in the cylindrical high tension electrode of the free air chamber, with its longitudinal centre line at the same focal distance as the centre of the collector electrode and passing through and lying perpendicular to the centre line of the beam By this experimental arrangement the readings of the instrument may be compared with those of the free air standard chamber without correction for differences in beam attenuation in air and without changing the position of the standard chamber If the instrument is later used with different lengths of its detector stem exposed to radiation, the corresponding correction for the variation in response with the stem length irradiated has to be applied A separate investigation of this variation is a necessary part of the test program to which for example cavity chambers have to be subjected before final calibration

The writer as early as 1930 in the first investigation of the free air standard chamber of this institute used a collector electrode divided into seven equal parts each of which was arranged to be independent of the others (ref 4) The quantity of electricity collected by each of these seven collectors could thus be measured separately The roentgen tube used was a Metwa Metalix having a thin glass window According to a separate investigation (ref 6) the glass window thickness of this tube was 0 33 mm which was found to be equivalent to 0 27 mm of aluminium With a tube voltage of 165 kV constant potential and no added filter, the HVL of the beam measured by the standard chamber was 0 055 mm Cu by an added copper filter the HVL was increased to 0 35 mm Cu Using these two beams measurements of the ionization were made separately by each of the seven collectors The results obtained are given in Table 4 The change in potential between the plates of the collecting precision capacitor, v is given in volt per minute The values in column 3 refer, however, to a capacitance of the collecting capacitor other than those in column 4 It is seen that v obtained with no added filter, is slightly reduced by absorption in the air along the collector electrodes This effect disappears with the added copper filter

If the v values in Table 4 are symmetrically added, and each sum divided by the corresponding collector length, we obtain the result shown in Table 5 It appears that $v/l$ is of good constancy at both the beams This verifies that it is correct to refer the measurement result to the centre of the collector electrode

## Acknowledgement

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## SUMMARY

Improvements of the Swedish roentgen standard laboratory equipment introduced in connection with an increase of its calibration capacity from 200 to 300 kV are described The employment of a sub-divided collector electrode as well as the characteristics of the new 300 kV tube and the new diaphragm system and precision measurements of diaphragms are discussed

## ZUSAMMENFASSUNG

Ein Ausbau der Kalibrierungsmoglichkeiten des schwedischen Röntgenstandardlaboratoriums von 200 kV auf 300 kV wird beschrieben Die schon fruher verwendete 7 teilige Messelektrode in der Standardkammer die Eigenschaften der neuen 300 kV Rontgenrohre und des neuen Blendensystems nebst Prazisionsmessungen einzelner Blenden werden ausfuhrlich erortert

## RÉSUME

Description de perfectionnements apportés a l équipement du laboratoire suedois des etalons roentgen en meme temps que sa capacite d etalonnage passe de 200 a 300 kV L auteur etudie l emploi d une electrode collectrice subdivisée ainsi que les caracteristiques du nouveau tube de 300 kV le nouveau systeme de diaphragme et les mesures de precision des diaphragmes

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# REPORT ON MEETING ON PRACTICAL METHODS OF ASSISTING RADIOTHERAPY CENTERS IN LESS DEVELOPED AREAS

## International Atomic Energy Agency/World Health Organization

## Montreal, Canada, September 4—6, 1962

In 1959 and 1962 the International Atomic Energy Agency and the World Health Organization jointly convened two meetings of experts in radiotherapy and radiation physics The first meeting was held in Vienna from 3—5 August 1959 the second in Montreal from 4—6 September 1962 Although the two meetings took place under different titles and with different participants they were both concerned with the development organization and practice of radiotherapy with particular reference to high energy radiation The Chairman of both meetings was Professor Sir Brian Windeyer

It was the intention of the 1959 Vienna meeting to produce basic recommendations which would be of value to all authorities responsible for radiotherapy in cancer treatment to those considering the establishment of radiotherapy centers and to practising radiotherapists and radiation physicists The recommendations of the meeting were drawn up with a view to giving practical guidance rather than as a contribution to fundamental knowledge on the subject

The recommendations of the 1959 meeting were published in various languages in a number of radiological journals and also in booklet form together with some background information, under the title Use of Radioisotopes and Supervoltage Radiation in Radiotherapy Present Status and Recommendations (International Atomic Energy Agency Vienna 1960 copies of the booklet are still available in English French Russian and Spanish)

The 1962 Montreal meeting was conceived as a follow up meeting in which the subject matter of the earlier meeting would be reconsidered with particular reference to the problems of developing countries Some of the topics which were mentioned only briefly in the first meeting were therefore dealt with in more detail together with other topics of special interest to developing countries

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## REPORT

### I Terms of reference

The deliberations of the working party were directed towards assisting developing countries in the application of radiation sources in cancer therapy

### II Introduction

It is desirable for a nation considering the establishment of radiotherapy centers to evaluate the overall needs of its people and to arrive at a decision as to the necessity for increasing its effort against cancer There is no doubt that radiation therapy is and may well remain an essential element in the medical effort to treat cancer patients and if a proper organization for the treatment of cancer is developed an efficient radiotherapy service is therefore essential

The recommendations made by this working party are based on the Report of the Study Group on the Use of Radioisotope Teletherapy Units and Supervoltage Radiation in Radiotherapy 1959 (Use of Radioisotopes and Supervoltage Radiation in Radioteletherapy Present Status and Recommendations IAEA Vienna 1960) The working party accepted

the organization detailed in the 1959 Report Parts I II and III as the basic minimum for an efficient radiotherapy service but considered that the following changes in emphasis are appropriate in the light of further experience with supervoltage therapy

(a) Caesium 137 or any other radioisotope emitting radiation of energy less than 1 MeV should not be regarded as a form of supervoltage Suitably designed caesium 137 units can however be used as substitute for orthovoltage X ray machines

(b) Greater emphasis should be placed on the need for physics services In addition to trained physicists who should be employed full time in radiotherapy attention should be drawn to the necessity for the provision of adequate physics laboratories and equipment

(c) Attention is drawn to the desirability of having relatively uncomplicated machinery for routine treatment where there are difficulties in adequate maintenance

## III The establishment of radiotherapy centers

A radiotherapy center should provide acceptable medical and scientific conditions for the treatment of cancer patients by means of radiation This can be done only if the center is related to the medical and scientific community as a whole because while radiotherapy is an essential medical element in the treatment of cancer it is not the sole means for so doing Co-operation with other medical specialities is therefore necessary Similarly continuing contact with the scientific community will ensure that appropriate scientific developments will be applied to the patients

In order to provide the necessary conditions for the practice of radiotherapy the radiotherapy service should be set up in close association with other clinical departments and also with the basic medical sciences It is therefore desirable that a radiotherapy center be placed within a medical teaching institute

The working party considers it important that a radiotherapy center should accept its responsibilities in the training of personnel at both undergraduate and postgraduate level Professional staff both medical and non medical should undertake the teaching and training of radiotherapy personnel Furthermore some instruction in radiotherapy should be given to all medical students so that they can be provided with an overall picture of cancer treatment Such *instruction would also encourage subsequent recruitment of radiotherapy trainees*

A radiotherapy center should also provide facilities for research and development work and professional staff both medical and non medical should be allowed and encouraged to participate in such research

The radiotherapy center must be in the charge of a radiotherapist The physical conditions of treatment with ionizing radiations are complex and their accurate planning and realization are essential for the patient if his cancer is to be controlled with minimal likelihood of damage to normal tissues and if the staff and public are to be guarded against overexposure to radiation The radiotherapist must therefore be assisted by a physicist responsible to him for all statements relating to the absorption of ionizing energy in the patient staff and the environment

The professional staff must furthermore be supported by technical staff such as radiotherapy and physics technicians, so that they may effectively discharge their responsibilities In addition it is important that an engineer or technician capable of maintaining and servicing apparatus and equipment be available at all times

## IV Responsibilities and duties of radiotherapy personnel

*A—Radiotherapist*

Since the most important part of a radiotherapist s work concerns the treatment of malignant diseases the following details refer specifically to his duties with respect to this type of disease.

1 *Clinical duties* The radiotherapist collaborates with his clinical colleagues in diagnosing the disease and in making the fundamental decision as to whether or not it should be treated by radiotherapy He is responsible for the medical care of the patient undergoing radiotherapy He is also responsible for ensuring that adequate records of the patient and his treatment are kept

2 *Treatment planning* The aim of treatment planning in radiotherapy is to irradiate a defined volume of tissue and to deliver to it a dose considered as optimum The radiotherapist is responsible for this task he is helped by physicists and technicians but his responsibility remains complete His minimum duties in treatment planning are the following

(a) Localization of tumour delineation of the target volume determination of the relation of the target volume to the external contour of the body in the treatment position and to neighbouring structures

(b) Choice of the type of radiotherapy e g external beam therapy or interstitial therapy

(c) Deciding the dose total absorbed dose in the tumour fractionation overall time and number of sessions

In some cases his work for treatment planning can be limited to these items Usually however in conjunction with the physicist he also chooses the best way of delivering radiation to the patient

After estimation of the absorbed dose within the body of the patient by the physicist he must satisfy himself as to the dose received by the radiosensitive tissues in order to be sure that none of them receive a dangerous dose

3 *Conducting the treatment* (a) Clinical examination of the patient at least twice weekly in order to judge the effects of the radiation (b) Overall verification of the technician s work especially as regards the positioning of patients before irradiation and the absence of any change of position during treatment

4 *Follow up of the patient after treatment*

5 *Radiation protection* The senior radiotherapist is responsible for protection of his staff against radiation

6 *Teaching and Research* As already indicated an important part of the radiotherapist s work may lie in the fields of teaching and research

*B—Physicist*

Generally speaking the responsibilities of the physicist fall into three categories services related to the treatment of patients teaching and research The amount of time he will spend on each of these will depend on the state of development of the radiotherapy department and the hospital with which he is associated

As minimum duties the physicist shall be responsible to the radiotherapist for

1 All aspects of radiation dosimetry
2 Collaboration in treatment planning
3 All physical aspects of radiation protection
4 All physical aspects of the use of radioisotopes
5 Design and construction of ancillary apparatus such as beam directing devices
6 Overall supervision of maintenance of equipment
7 Advice on the choice of new radiotherapy and radioisotope equipment and building design problems

*C—Radiotherapy technician*

In general the duties of the radiotherapy technician are to assist the radiotherapist to plan and execute the treatment of the patients and to record relevant information concerning the treatment The radiotherapy technician is directly responsible to the radiotherapist for these duties which may include

1 Assisting the radiotherapist in the day to-day treatment of the patient including positioning the patient for treatment verification throughout the irradiation that the desired position is maintained and otherwise assisting the radiotherapist as required in the care of the patient

2 Preparing equipment for daily use for example warming up X ray machines calibrating treatment units (under the general direction of the physicist) and recording the value obtained

3 Using beam directing aids including field localizing films

4 Assisting the radiotherapist in the preparation and use of positioning aids such as body cast moulds etc

5 Maintaining records of the factors of treatment These will include statements of exposure dose treatment time relevant calculations etc

6 Assisting the radiotherapist in the therapeutic use of sealed and unsealed radioisotopes

## V Working conditions

As already emphasized radiotherapy should be carried out within the general framework of medical and surgical services and should be closely integrated with other branches of medicine The aim should be to develop a system whereby the radiotherapist is a competent clinician who is a full partner in the team work necessary for the treatment of cancer He should be sufficiently trained and of such caliber as to have clinical control of patients and be able to have hospital beds under his own control

In view of the variety and technical nature of the tasks which the radiotherapist must perform and the grave handicap which a dispersion of his activities among various occupations presents both for him and his center it is desirable that as far as possible he should devote his full time to radiotherapy in a single place of work To this end adequate remuneration must be provided In this way will it be possible to gain the maximum value from the personnel and equipment of a radiotherapy center

The physicist must be recognized as a full working partner with the radiotherapist He must be given facilities which will allow him not only to meet the day to-day clinical needs of the department but also to make fundamental contributions to the treatment of cancer by radiation To this end he must have

(a) Adequate laboratory space and instrumentation

(b) Machine shop facilities

(c) Competent technical assistance as the development of the department merits

(d) Opportunity for research

In order to attract a man of suitably high caliber the salary and career prospects must be commensurate with those obtained in comparable scientific positions

Adequate library facilities and the opportunity to attend meetings are also essential to all personnel

## VI Training and assistance

Training of staff is one of the greatest problems in the building up of radiotherapy services The following lines of approach are considered to be important

*A—Fellowships*

It is recognized that effective operation of a fellowship programme is one of the best means of achieving improvement in radiation therapy. It is urged that the number of fellowships in radiotherapy and radiation physics be increased and their existence made known on a wide scale. The working party agreed that the operation of the fellowship programme should be integrated with the overall planning leading to the establishment or development of a center for radiation therapy.

The fellowship programme should include opportunities for training for persons with no prior experience in radiotherapy or radiation physics as well as arrangements for shorter periods of time for persons whose qualifications may range up to and include full competence in their field and who wish to obtain experience in a special facet. A training grant may be necessary for a few months only or may be required for a three year period in the case of a person who needs full training.

As noted in the 1959 report, the larger teaching centers in all countries should recognize an obligation to assist the sponsoring organizations to train individuals in this field.

In the course of the discussion of the working party on fellowship training, a number of practical points emerged. Although these matters are already known to the IAEA and WHO it was considered worthwhile to bring them forward again for the sake of emphasis.

1. *Language barriers.* It is necessary that a Fellow who is to receive all or most of his radiotherapy training have a good working knowledge of the language of the country to which he is assigned. If this condition is not satisfied the value of the training is reduced. This is particularly true for medically qualified Fellows, since ability to communicate easily and accurately with patients is essential to their training.

2. *Early communication between trainee and training center.* It is suggested that, in all cases, the trainee be urged to write to the prospective training center at as early a date as possible and that the training center should communicate with him. This would allow an interchange of ideas about his desires and needs and permit the center to recommend reading material. Much time could thus be saved both by better definition of his training programme and by prior acquisition of basic knowledge. The early contacts will facilitate the definition not only of the programme but also of the length of the fellowship.

3. *Level of knowledge.* It is unfortunately true that the level of knowledge presumed by the sponsoring organization and by the training center is not in fact always met by the trainee. As mentioned above, early communication between the trainee and the institution responsible for the training would do much to clarify this point. In some instances it may be necessary to revise the proposed programme in such a way as to render it appropriate to the candidate's actual level of knowledge. The decision should rest with the training director who may also recommend, if necessary, that the period of training be extended.

4. *Assurance of a position after completion of training.* It is recognized that this is a difficult problem. Many training centers have had the unhappy experience of training excellent Fellows who, upon return to their home countries, have found no suitable positions. This problem is such a serious one, both for the Fellow and for the training institution, that it is felt that fellowships in radiotherapy should not be granted unless a suitable post is assured for the returning Fellow.

The sponsoring organizations should therefore seek by all appropriate means assurance that the interested governments understand the gravity of this problem and the need for making every effort to ensure suitable working conditions for the trainee on his return, which may include the provision of certain necessary items of equipment.

5 *Timing of fellowships* Many centers which accept Fellows have organized training programmes which begin at a certain period of the year It is urged that in such cases fellowships should be timed so as to fit in with these programmes Otherwise months may be wasted and the value of the fellowship considerably reduced

6 *Selection of Fellows* The number of candidates for fellowships in radiotherapy and radiation physics may well exceed the number of available fellowships It is clearly desirable to assure the greatest efficiency in the fellowship programme and it is therefore desirable that great care should be given to ensuring a wide geographical distribution of the candidates and to the difficult task of selecting the best recipients both on a national and international basis

### B—Visiting experts

These represent a very important form of assistance and must be encouraged They must be integrated in a more general programme of international aid Advanced countries and institutes should be urged to provide facilities for their staff to participate in such programmes

There are two main categories of visiting experts Long visits i e of several months will enable a broad new field of work to be initiated short visits of experts will point to the direction in which a special effort is needed and will help the experts themselves to understand the problems of the centers visited and to guide the work of those who may subsequently receive fellowships

### C—Co-operation and exchange of personnel between institutes

Schemes of co-operation between individual institutes either within a given country or in different countries appear to be a particularly good way of providing training facilities on the one hand and unusual scientific or clinical material on the other The working party draws attention to the possibility of the sponsoring organizations acting as intermediaries in arranging such co-operation It is expected that the arrangements will include the exchange of professional and technical personnel between the two centers It is suggested that such exchange should be arranged either as a follow up to the visit of an expert from one center to the other or in the course of a programme of co-operation between the two centers

### D—Training courses

The working party recognized that a formal training course of some weeks or months duration and organized on a national regional or international basis can be of value provided it is realized that a short course cannot replace the more lengthy training in a radiotherapy institute which is required to produce qualified radiotherapists and radiation physicists Short courses may however perform a useful function in giving advanced training in certain fields to already qualified personnel

### E—Regional advisers

The working party agreed that the appointment of radiotherapists and radiation physicists as regional advisers would be valuable in many regions of the world These advisers should be appointed on a long term basis for the purpose of helping and advising all the radiotherapy centers within a defined geographical region Such personnel should be carefully chosen having regard to their technical and personal qualities

### F—Regional symposia

The working party considered that the holding of regional symposia should be encouraged Such symposia on both medical and physical aspects of radiotherapy would be of benefit to all personnel in less-developed regions of the world and would foster co-operation in these areas

# BOOK REVIEW

Die Interne Krebstherapie. Von H. D. Diamond. Deutsche Übersetzung von P. Obrecht und P. Berg. 158 Seiten, 42 Abbildungen und 23 Tabellen. Georg Thieme, Stuttgart 1960. Price DM 29.50.

It is becoming increasingly necessary for clinicians to have access to an informative review of the chemical agents available for the treatment of malignant disease. Thousands of new substances are tested each year for their carcinoid effect although only a few are submitted for clinical trial and even fewer gain clinical use. It is widely accepted that malignant disease cannot be cured by chemical agents but this does not necessarily mean that the course cannot be influenced by medication. Clinically useful chemotherapeutic agents and hormones are already available in such large numbers that much confusion and uncertainty exist regarding their fields of application and dosage. Insufficient knowledge concerning these substances results in their not being so widely used as they should be in the palliative treatment of neoplasms.

Thieme's Publishing House has issued "Die interne Krebstherapie", a German translation of the original work "The Medical Management of Cancer", published in America in 1958 and written by H. Diamond, who has had wide experience in this field. The book deals with a number of malignant diseases — one chapter for each — that have often proved to respond to chemotherapeutic and hormonal methods of treatment. Malignant lymphomas and leukemias are afforded pride of place but other types of malignancy, such as mammary and pulmonary carcinoma, are also included. Attention is mainly concentrated on chemotherapy and hormonal treatment while intracavitary radiologic treatment is mentioned only for information; intracavitary radioisotope therapy is however given a special exhaustive chapter by two radiotherapists.

This readable book contains interesting information not only on the treatment of different diseases but also *on their symptomatology and variations. No objections* can be raised to the methods of treatment described although other forms might in certain cases prove equally satisfactory. The procedures are competently and simply described, usually with reference to original publications. The work is somewhat biased, as the author refers almost exclusively to experiences reported in the Anglo-Saxon literature; this has been rectified to some extent by the publishers who have added a list of German publications to the references given for each chapter. The brief descriptions of radiologic treatment methods are largely in accordance with the methods and doses used in Sweden.

The book should be of interest to all clinicians who deal with cases of malignant disease. Despite its age it is still of great value in practice, seeing that many years of clinical trials are necessary before a new preparation can be put on the market for general use. A few substances fairly generally employed in recent years (e. g. cyclophosphamide-endoxan and phenylalanine mustard — Melphalan, Sarcolysin, PAM) are however missing. Nor is there any mention of more recent forms of administration, such as perfusion and continuous intra-arterial infusion, although admittedly these are methods that are not yet ripe for general clinical use.

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# VERSATILE POSITIONING AID IN FIXED AND MOVING FIELD THERAPY IN HEAD AND NECK TUMORS

by

RUHERI PEREZ TAMAYO and CHARLES E SEIBERT

In this progressive era of rapid medical advancement and development of more precise treatment techniques it is remarkable that so little attention has been given in the literature to the importance of immobilization of the head and neck for radiotherapy of tumors of these areas (see list of references) The necessity for immobilization may be obvious yet publications concerning how to achieve this point are very rare indeed In no other part of the human body is immobilization so critically vital The extreme radiosensitivity of the uninvolved eye is only one of the many self evident examples of the crucial need for complete immobilization while treating the head Fortunately this is one part of the human body where motionlessness can be obtained very effectively Thus the radiotherapist should provide precise means to hold the head and neck of the patient

Not only children but comatose unconscious disoriented or uncooperative patients need to be treated while properly restrained The treatment of the most cooperative patient can be unsatisfactory due to insensible involuntary movement since the final dose distribution depends on the position of the field and the position of the field depends on the position of the part of the body under treatment

From the Department of Radiology Division of Radiotherapy (Director Prof R Perez Tamayo) University of Colorado Medical Center Denver 20 USA Submitted for publication 12 November 1962

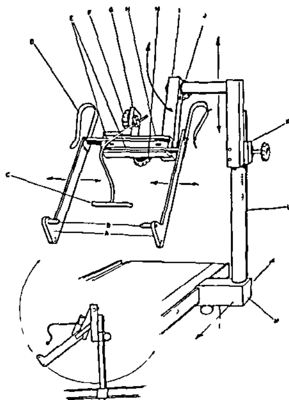


Fig 1

A — Ear support arms
B — Ear pieces
C — Vertical extension stabilizer bar
D — Cassette clip
E — Lateral adjusting racks
F — Stabilizing clamping bracket knob
G — Stabilizing clamping bracket
H — Lateral adjustment rack housing
H — Rack pinion adjusting knob
I — Swivel yoke
J — Swivel yoke locking knob
K — Elevating pinion
L — Calibrated upright
M — Table clamp

Immobilization therefore, is also important because it is intimately related to accurate field placement Over and above the inherent limitation of the ability to recognize the exact localization and extent of certain lesions the head and neck lends itself to many informative examinations and better localizations Ventriculograms, pneumoencephalograms, arteriograms and other special procedures are good examples of the vast diagnostic aids available to the radiotherapist when in search of guiding points for the field placement in the treatment of brain lesions Indirect laryngoscopy soft tissue technique roentgenograms of the neck and tomograms are good examples of diagnostic procedures invaluable in the localization of the lesions of the neck

Once the reasonable localization of a lesion has been accomplished treatment fields can be oriented accordingly and related to reference points The unchangeable orbitomeatal base line may be used as a constant reference (cf Fig 2) This line maintains its relative position in the head at any degree of flexion of the neck and permits treatment reproducibility The correct initial field adjustment can be checked with placement films and the entire procedure may be repeated daily, without error if the known position of the fields relative to the base line and the known position of the source relative to that of the



Fig 2 Patient and head holder in position o bi tomeatal line drawn in black

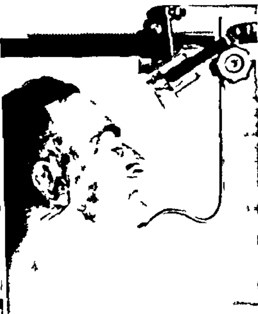


Fig 3 Patient (lying horizontal) and head holder in position for treatment of neck lesion

head or neck are kept constant Unless this is done localization and placement are useless

In the Division of Radiotherapy at the University of Colorado Medical Center the localization and routine placement films of the fields as well as the immobilization of the head and neck are accomplished with a specially designed positioning aid or head holder

Allowing for the need and desirability of such a positioning aid or head holder certain features are then necessary for optimum function and performance

1 The unit must be adaptable for the treatment of either head or neck lesions yet not be in the path of the primary treatment beam because then in the primary treatment beam the skin sparing effect of high energy radiations will be lost and the intensity of medium voltage range will be seriously reduced

2 It must be portable but sturdy Portability is an important feature in that an unwieldy heavy immobilizer might find itself more frequently in a storage area than readily available in the treatment room Durability and strength are however necessary features

3 It should be accurate but simple in design and operation to assure speed in the daily treatment of patients

4 It should have provisions to facilitate film localisations



Fig 4 Example of setting with film cassette in position for localization film

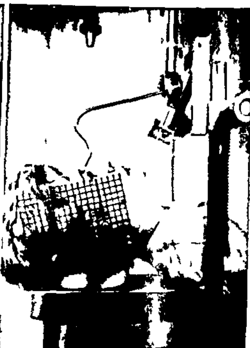


Fig 5 Metallic grid fitting on head holder: alignment of grid line with orbitomeatal line

5 Finally it should afford daily accurate reproducibility of treatment fields by either physician or technician

Following the basic principles of the device used by Dr Isodore Lampe at the University of Michigan, a unit was designed with added features to fulfill the particular needs of the treatment center at the University of Colorado Medical Center The head holder designed and built for our division of radiotherapy, is depicted in Fig 1

Functionally, it can be divided into five parts

1 The calibrated upright part (I) with elevation rack fastened to the treatment table by a table clamp (M) This can be easily moved along the table and will meet the head at variable distances it is equipped with a scale which designates the position For treatment of head lesions this upright part is used as depicted in Fig 2 and for treatment of neck lesions it is placed as depicted in Fig 3 The unit, however, can be fastened on the right or left side in either case Note that the head holder will not be in the way of the source housing while moving therapy is employed thus avoiding possible collision When not in use, the upright part and the head holder are conveniently stored on a similar clamp on an adjacent wall or table

2 The elevating pinion (K) fits on the calibrated upright and by turning the

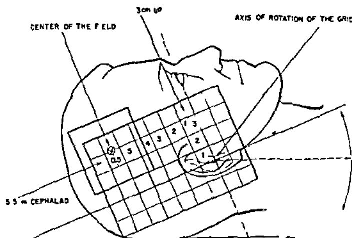



Fig 6 Example of setting of field using grid co-ordinates The selected center of a treatment field is 3 cm up and 5 5 cm cephalad from the zero point (These figures are derived from localization field film ) These distances are counted off on the grid and the central beam and cross hairs are moved to coincide with this point Field size is then limited to the desired dimensions

elevating pinion knob the pinion can be elevated or lowered to any desired height

3 The swivel yoke (I) is attached to the elevating pinion and is free to pivot *in a rotary fashion as shown in Fig 1 It is locked into any desired position by* the swivel locking knob (J) The lateral adjustment rack housing (H) is attached to the swivel yoke The housing contains lateral adjusting racks (E) which are moved inward or outward by the rack pinion adjusting knob (H¹) Ear support arms are attached to the adjustment rack and ear pieces (B) are attached to these

4 A flexion extension stabilizer clamping bracket (B) and stabilizer clamping bracket knob (F) hold the vertical extension stabilizer bar (C)

5 Accessory features include cassette clips (D) for cassette holding which are attached to plastic ear support arms holes present in the ear pieces to permit accurate placement into the auditory canals and a plastic grid with metal cross hatch grid which will fit into the ear holder pieces (see Fig 4)

The use of the head holder is best described by one example the positioning of a patient for the treatment of a brain tumor The patient assumes a comfortable supine position on the treatment table Any comfortable flexion or extension of the neck can be used for the treatment of brain tumors because the final setting is based on the orbitomeatal line and this reference remains the same with flexion or extension of the neck This feature of the head holder is especially

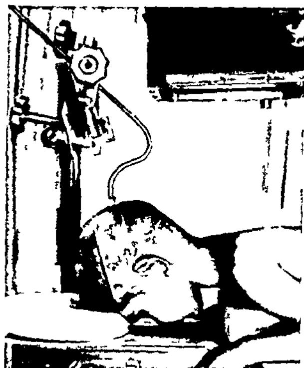


Fig 7 Example of use of head holder in treatment of posterior field in child with medulloblastoma

rewarding in short necked patients or those with arthritic changes which would limit their ability to assume a forced position The general position is that of the patient shown in Fig 2 The elevating pinion is lowered or elevated until the plastic ear pieces are at the level of the auditory canal Combined adjustments of the elevating pinion and the pivoting movement of the swivel yoke facilitate this preliminary step The ear support arms are approximated by turning the rack pinion adjustment knob until the ear pieces fit into the auditory canals and the head is held snugly The pressure maintained by the ear pieces and supporting arms need not be great Indeed it was quite surprising to observe the small amount of pressure needed to stabilize semicomatose patients and potentially uncooperative pediatric cases The mere sensation of the ear pieces in place, while not uncomfortable seems to promote immobilization The flexion extension stabilizer bar is then adjusted to one of a number of selected sites to maintain a given degree of neck extension Examples of selected sites might be the forehead the bridge of the nose, the anterior nasal spine or the chin Here, again pressure is not demanding but only a gentle reminder for the patient not to move The fields can then be adjusted The position of the upright part the height of the elevating pinions and the angle of the swivel

yoke are calibrated and may be charted so as to duplicate the entire setting daily

For accurate daily fields, portal placement, one needs an unchanging base line point It was mentioned earlier that an excellent built in base line is available in the head, i e the orbitomeatal line as depicted on Fig 2 Since this line is unchanged by a degree of flexion of the head or neck, daily accurate field portal reproducibility can be achieved by locating the center of a given treat ment field at a perpendicular distance from this line To accomplish this a plas tic grid with opaque grid lines is placed on the ear support arm and rotated until the central grid line coincides with the orbitomeatal line (Fig 5) The intersection of the cross hairs of the light localizer of the source is made to coincide with the meatus of the ear Then the collimator is rotated until the cross hairs are superimposed over the orbitomeatal line and the central grid line as in Fig 6 This constitutes the zero position A roentgenogram is obtained *making use of the treatment source with the head or neck in the* treatment setting and the center of the field can then be determined on the film Its position and size can be noted by taking co-ordinates on the grid from the zero point (The localization film technique is fully described in another publication ) Using the co ordinates from the zero point, the central beam is then moved to the selected central field position Once more the grid and the cross hairs permit the easy placement and alignment of the center of the beam onto the predetermined center point of the field The superimposition of the cross hairs and grid is simple

As shown in Figs 3 and 6 the head holder is easily adapted for lateral anterior or posterior neck portals, with the patient prone or supine In these areas the vertical extension flexion stabilizer is again of prime importance Since in the treatment of anterior neck lesions elevation of the chin is imperative to thrust the soft tissue structures of the neck as far anteriorly as possible this feature is again important As depicted in Fig 3 full extension can be in sured and a neck field can be constructed and adjusted without compromis ing the cervical cord

Needless to say, the accuracy required for moving field therapy is easily accomplished with this unit

## Acknowledgements

This work was supported in part by a Bent County Cancer Fund grant and grant CRT 5084 from the National Cancer Institute National Institutes of Health

The assistance of Mr Richard Raper mechanical engineer is gratefully acknowledged

## SUMMARY

The need and features of a head stabilizing aid for treatment of head and neck tumors is discussed A lightweight versatile head holder designed to fulfill the needs of immobilization film localization and accurate daily field placement is described A simple method of achieving daily reproducible treatments is presented using the orbitomeatal line as a constant baseline

## ZUSAMMENFASSUNG

Die Notwendigkeit wie auch das Aussehen eines Kopfstabilisators zur Behandlung von Schadel und Nackentumoren wird besprochen Ein leichter drehbarer Kopfhalter zur Immobilisierung Filmplazierung und exakter Feldeinstellung wird beschrieben Es wird eine einfache Methode fur taglich wiederholbare Behandlungen gezeigt wobei die meatus-orbital Linie als Basislinie verwendet wird

## RÉSUMÉ

Les auteurs examinent l utilité et les caractéristiques d un moyen de contention pour le traitement des tumeurs de la tête et du cou Ils décrivent un craniostat léger maniable construit pour permettre l immobilisation la localisation du film et la mise en place quotidienne précise du champ Ils presentent une méthode simple utilisant la ligne orbito-auriculaire comme ligne de base constante pour obtenir un traitement reproductible quotidien

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Wiernik G A new radiotherapy treatment chair Brit J Radiol 34 (1961) 676

FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL), UNIVERSITY OF CAMBRIDGE, ENGLAND

# EFFECT OF BREATHING HIGH PRESSURE OXYGEN UPON TISSUE OXYGEN TENSION IN RAT AND MOUSE TUMOURS

by

D B CATER, E L SCHOENIGER and D A WATKINSON

The tissue oxygen tension is an important factor in the radiosensitivity of tumours (CRABTREE & CRAMER 1933 MOTTRAM 1935, 1936, HOLLCROFT LORENZ & MATHEWS 1952 GRAY CONGER, EBERT, HORNSEY & SCOTT 1953, GRAY 1957) Tissues with an oxygen tension greater than 10 mm Hg are about twice as radiosensitive as tissues with an oxygen tension of less than 0 5 mm Hg (GRAY 1961) Because of the rapid cell division in tumours and the anatomical and physiological abnormalities of the blood vessels (CATER GRIGSON & WATKINSON) zones of necrosis are frequently seen Adjacent to these necrotic areas there are viable tumour cells living under sufficiently anoxic conditions to be relatively radioresistant (THOMLINSON & GRAY 1955) These cells might need 9 000 r to kill them compared with 4 000 r for well oxygenated cells (WRIGHT 1962) It is believed that such anoxic radioresistant cells are an important cause of the recurrence of tumours after radiotherapy

Practical attempts to deal with this problem have followed four patterns

1 To raise the anoxic zones of the tumour to full radiosensitivity by inhalation of oxygen at atmospheric pressure HULTBORN & FORSSBERG (1954) studied the effect on tumours of the skin and MITCHELL (1957 (a) (b), 1960) has used oxygen as a radiosensitiser since 1953

Submitted for publication 11 October 1962

## ZUSAMMENFASSUNG

Die Notwendigkeit wie auch das Aussehen eines Kopfstabilisators zur Behandlung von Schädel- und Nackentumoren wird besprochen. Ein leichter drehbarer Kopfhalter zur Immobilisierung, Filmplazierung und exakter Feldeinstellung wird beschrieben. Es wird eine einfache Methode für täglich wiederholbare Behandlungen gezeigt, wobei die meatus-orbital Linie als Basislinie verwendet wird.

## RÉSUMÉ

Les auteurs examinent l'utilité et les caractéristiques d'un moyen de contention pour le traitement des tumeurs de la tête et du cou. Ils décrivent un craniostat léger maniable construit pour permettre l'immobilisation, la localisation du film et la mise en place quotidienne précise du champ. Ils présentent une méthode simple utilisant la ligne orbito-auriculaire comme ligne de base constante pour obtenir un traitement reproductible quotidien.

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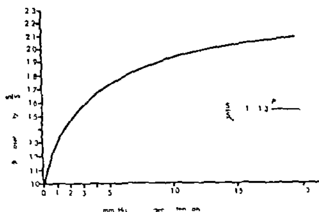


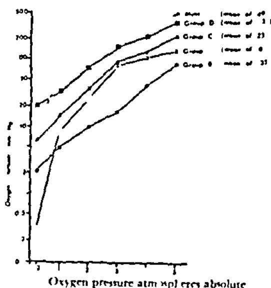
Fig 2 Relationship between radiosensitivity and oxygen tension on the formula of GRAY (1961)

## Materials and Methods

The tumours used were spontaneous mammary carcinomas in mice of C3H strain Jensen sarcomas in white Wistar rats and transplantable hepatomas in rats of the August strain The rat tumours were transplanted into the muscles of the thigh which produced excellent tumours infiltrating muscle and permitted complete immobilisation of the tumour site during the experiment Tumours transplanted into the subcutaneous tissues of the flank were less satisfactory

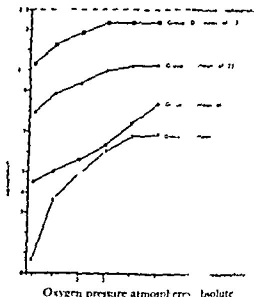
The rats and mice were anaesthetised with urethane 7 5 ml kg of a 20 % w/v solution injected subcutaneously In the later experiments tracheotomy and carotid cannulation were performed prior to insertion of electrodes Less than 0 1 ml of heparin (5 000 I U /ml) was mixed with the saline in a polythene cannula which was tied into the carotid artery The blood pressure was measured with a Borden type pressure gauge with a 5 cm diameter dial This was calibrated against a mercury manometer The dimensions of the oxygen pressure chamber were too small for a mercury manometer to be used

The animal was fixed to the table A of the pressure chamber (see Fig 1) and the electrodes were inserted and connected to the amplifiers Measurements of oxygen tension with the animals breathing air were made by the oxygen cathode technique using the apparatus described by CATER SILVER & WILSON (1959) using rhodium plated stainless steel electrodes described by CATER & SILVER (1961) Recordings were made by the simple device described by CATER GRIGSON & WATKINSON (1962b) The perspex cylinder (B in Fig 1) was slid into place and the chamber was sealed against an O ring by tightening three winged nuts Oxygen at atmospheric pressure was administered



Oxygen pressure atmospheres absolute

Fig 3 Log of mean oxygen tension in tumour plotted against the pressure of oxygen inhaled by the animal Groups according to the initial oxygen tension with animal breathing air group A 0 to 0 5 mm Hg group B 0 5 to 4 mm Hg group C, 4 to 10 mm Hg group D more than 10 mm Hg



Oxygen pressure atmospheres absolute

Fig 4 Mean radiosensitivity of tumour sites in each group plotted against pressure of oxygen inhaled by animal The groups are the same as in Fig 3 and Tables 1 and 2

with the chamber closed but with the pressure release valve C open After 5 minutes this valve was closed and the pressure steadily raised through a reduction valve on the oxygen cylinder The safety valve D was set to open at 4 atmospheres excess pressure (5 atmospheres absolute) In a typical experiment the following observations were made the oxygen tension of tumour and muscle, rectal temperature, mean carotid blood pressure pressure of oxygen in the chamber, and notes on the general condition of the animal The animal s temperature was controlled by an external heating lamp and by running hot or cold water through the coil of copper tubing F in the lower part of the chamber In experiments on cerebral oxygen tension the rat s head was held in the stereotaxic instrument, F mounted in the chamber, and the electrode was lowered into the brain to a known depth below the dura by a micrometer screw M through a burr hole in the skull 1 to 3 mm caudally and 1 mm laterally to bregma At the end of the experiment the rat was killed with chloroform and fixed by injecting 30 to 40 ml of 10 % formaldehyde in normal saline into the tail vein or carotid artery Next day the tumour with the electrodes still in situ was placed in formaldehyde saline for further fixation The electrodes were removed when the tissues were dehydrated and ready for embedding in wax Serial sections through the electrode site were made to study the tumour adjacent to the electrode

Macroscopic and histological examinations of the lungs, liver and kidneys of the animals were also made.

Serotonin (5 hydroxytryptamine creatinine sulphate supplied by Light & Co Ltd) was dissolved in physiological saline and used in a dose of 5 mg of base/kg I.P. Cyproheptadine (1 methyl 4 5 dibenzo [a, e] cycloheptatrienylidene piperidine hydrochloride monohydrate), or Periactin 1 mg/ml was kindly supplied by Dr J. J. F. Merry of Merck Sharpe and Dohme of Hoddesdon.

## Results

### *Assessment of useful increase of radiosensitivity of tumour with increase of pressure of inhaled oxygen*

The first analysis of the data was made as follows.

The results from the three types of tumour were pooled, giving electrodes in 77 different tumour sites for which there was good histological evidence that the tip of the electrode was situated in tumour. These electrode readings were divided into four groups according to their initial value with the animal breathing air. Group A, with an initial oxygen tension below 0.5 mm Hg, group B between 0.5 and 4 mm Hg, group C 4 to 10 mm Hg, and group D, above 10 mm Hg. The rationale of this grouping follows from the formula relating oxygen tension to radiosensitivity given by GRAY (1961)

$$\frac{S}{S_N} = 1 + 1.3 \frac{\text{Oxygen tension}}{\text{Oxygen tension} + 4}$$

where S is the sensitivity at the stated oxygen tension and $S_N$ is the sensitivity in nitrogen.

A plot of this formula is shown in Fig. 2. An oxygen tension below 0.5 mm Hg is believed to give a radiosensitivity not significantly different from the anoxic radiosensitivity of 1. An oxygen tension of 4 mm Hg gives a sensitivity of 1.65, i.e. half way to maximum radiosensitivity which is taken as 2.3. An oxygen tension of 10 mm Hg gives a radiosensitivity of 1.95. Fig. 3 shows the rise of mean oxygen tension of each group as the pressure of inhaled oxygen was raised from 0.2 to 5 atmospheres absolute. The oxygen tension is plotted on a log scale. The tumour oxygen tension obtained from each electrode at each pressure level of inhaled oxygen expressed in atmospheres was then converted into its equivalent radiosensitivity. A change of radiosensitivity of 0.2 was arbitrarily chosen as a significant increase or decrease for the purpose of scoring, and on this basis Table 1 was constructed.

It will be seen from this table that over half the tumour zones investigated showed an oxygen tension of less than 4 mm Hg when the anaesthetised rats and mice were breathing air. When the animals breathed oxygen at atmospheric pressure 16 electrodes showed an increase of radiosensitivity of 0.2 or more and one electrode showed a decrease. On the basis of one plus for every

**Table 1**

*Number of tumour sites in each group which would have an increase of radiosensitivity of 0.2 or more*

| Group | Initial oxygen tension in animal breathing air mm Hg | Initial radiosensitivity | Change of pressure of inhaled oxygen (in atmospheres absolute) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 0.2 to 1 | 1 to 2 | 2 to 3 | 3 to 4 | 4 to 5 | 0.2 to 5 |
| A | 0 to 0.5 | 1.00 to 1.00 | 2 [illegible] | 1 [illegible] | 1 [illegible] | 0 [illegible] | 0 [illegible] | 3 6 |
| B | 0.5 to 4 | 1.00 to 1.[illegible] | [illegible] 1 / 35 | 4 [illegible] / 35 | 3 / 34 | 7 / 31 | [illegible] / 31 | [illegible]3 4 / 35 |
| C | 4 to 10 | 1.[illegible] to 1.93 | 8 / 23 | 1 / 23 | 2 / [illegible]3 | 3 / 23 | 2 1 / [illegible]3 | 16 3 / 23 |
| D | 10 to 40 | 1.93 to 2.18 | 0 13 | 0 13 | 0 13 | 0 13 | 0 13 | 13 |
| Total all groups | 0 to 40 | 1.00 to 2.18 | 16 1 / 77 | [illegible] 1 / 77 | [illegible] / [illegible] | 10 / [illegible] | 9 [illegible] / [illegible] | 49 7 / 7[illegible] |
| Total net scores[1] | 0 to 40 | 1.00 to 2.18 | [illegible] | 10 | 10 | 15 | 13 + | 111 + |

[1] A rise of radiosensitivity of 0.2 counts one +, a fall of 0.2 counts one −

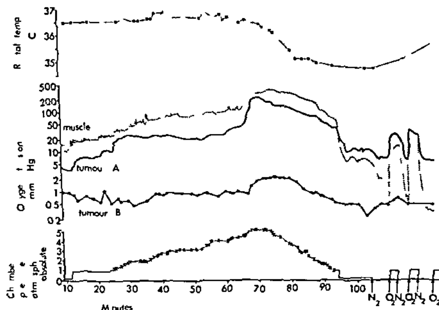
0.2 increase of radiosensitivity the score was 26 + after subtracting one negative response. The table shows that the change from air to oxygen at 1 atmosphere scores most heavily but that useful increases of radiosensitivity occur even up to 5 atmospheres absolute. A plot of the mean radiosensitivity indicated by the electrodes in each group at the different pressures of inhaled oxygen is shown in Fig. 4.

Another important consideration is the number of tumour sites which have reached near maximum radiosensitivity at each pressure level of inhaled oxygen

**Table 2**

*Number of tumour-electrodes showing near maximum radiosensitivity (equivalent to venous oxygen tension i.e. 40 mm Hg) with the anaesthetised animal breathing oxygen at various pressures*

| Group | Initial tumour oxygen tension | Pressure of inhaled oxygen in atmospheres absolute | | | | | | Total number of electrodes |
|---|---|---|---|---|---|---|---|---|
| | | 0.2 | 1 | 2 | 3 | 4 | 5 | |
| A | 0 to 0.5 | 0 | 1 | 1 | 2 | 2 | 2 | 6 |
| B | 0.5 to 4 | 0 | 1 | 1 | 3 | 6 | 13 | 35 |
| C | 4 to 10 | 0 | 2 | 7 | 10 | 13 | 17 | 23 |
| D | 10 to 40 | 1 | 5 | 7 | 10 | 11 | 13 | 13 |
| Totals A B C D | | 1 | 9 | 16 | 25 | 32 | 45 | 77 |
| Percentage | | 1.3 | 10.7 | 20.7 | 32.5 | 41.5 | 58.3 | 100% |




Fg 5 Record of experi nent 23 rat with Jensen sarcoma showing oxygen tens on plotted on a log scale in two tumour sites A and B and muscl

For this purpose, an oxygen tension of 40 mm Hg was taken This is equal to the oxygen tension of venous blood when air is breathed and corresponds to a radiosensitivity of 2 18 The data are shown in Table 2 and indicate a steady increase in the number of tumour sites reaching near maximum radiosensitivity as the pressure of inhaled oxygen was raised

*Relative importance of time under pressure versus height of pressure for obtaining a useful increase of radiosensitivity*

If pressure chambers are to be widely used in radiotherapy an important practical consideration arises whether a longer time at a lower pressure will be as effective as a short time at a higher pressure An attempt was made to obtain information on this point and during the first third of this series of experiments *the animals were held at each pressure level for the comparatively long* period of 5 to 10 minutes Such an experiment is shown in Fig 5

The tumour site A, showed a useful increase of oxygen tension when oxygen was inhaled at atmospheric pressure and at two atmospheres absolute near maximum radiosensitivity was reached The response was quick and no useful increase would have been obtained by the 5 minutes oxygen inhalation at 3 atmospheres absolute pressure

The tumour, site B with an initial oxygen tension of 0 5 to 1 mm Hg required the inhalation of oxygen at 5 atmospheres absolute before a useful response

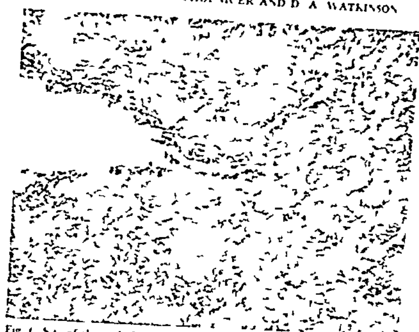


Fig 6 Site of electrode B in experiment 23 Fig 5 Jensen sarcoma with some dilated capillaries and some whorls of loose fibroblast like cells where tumour cells have degenerated H and E ×55

was obtained The inhalation of nitrogen and then oxygen at the end of the experiment gave rapid responses in muscle and tumour at site A but had little effect on tumour at site B The site of this latter electrode is shown in Fig 6 There are many viable tumour cells (Jensen rat sarcoma) near the electrode tip but there are also dilated capillaries and small pale areas where tumour cells have degenerated and been replaced by loose whorls of fibroblast type cells

Another experiment of this series is shown in Fig 7 but the tumour is a transplantable hepatoma The electrode in the tumour (see Fig 8 for histology) showed a low oxygen tension which increased markedly when oxygen was breathed at two atmospheres absolute The electrode in connective tissue between the tumour and the muscle showed a high oxygen tension when air was breathed An interesting finding was the rather slow fall of oxygen tension in the tumour when air breathing was resumed after the inhalation of oxygen at high pressure This was frequently observed When these experiments were compared with those in which the pressure was raised more rapidly (rising 1 atmosphere in 2 minutes and remaining 2 minutes at each pressure level see the first parts of Figs 9 to 13) it is clear that a short period of oxygen inhalation at high pressure was more effective in raising tumour oxygen tension than a long period of oxygen inhalation at low pressure

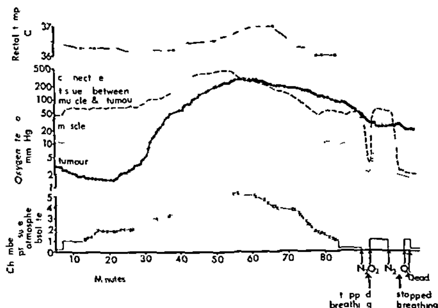



Fig 7 Experiment 24 rat with transplantable hepatoma Electrode in connective tissue between muscle and tumour – muscle and in tumour — — The oxygen tension in tumour remains high when breathing air after the inhalation of high pressure oxygen

*Importance of factors which alter the blood flow through tumour*

1 *Changes of systemic blood pressure* The pressure of inhaled oxygen is only one of the factors upon which tumour oxygen tension depends another important factor is the tumour blood flow CATER et coll (1962b) have shown that tumour oxygen tension is often dependent upon systemic blood pressure and that a fall of systemic blood pressure usually causes a marked fall in tumour oxygen tension In view of this finding and because it was suspected that inhalation of oxygen under pressure might shock the animals the systemic blood pressure was measured in the latter half of this series of experiments However during the periods of inhalation of oxygen under pressure a considerable increase of mean systemic blood pressure was always observed (see Figs 9 12 13, 14) Thus some of the increase of tumour oxygen tension during oxygen administration under pressure is due to this rise of systemic blood pressure causing an increase of blood flow through the tumour

2 *Effect of 5-hydroxytryptamine* Because of its action as a radioprotector CATER et coll (1962b) investigated the action of 5 HT on tumour oxygen tension They found that 5 mg/kg I P caused a more rapid and profound fall of oxygen tension in tumour than in bone marrow spleen and muscle and that the rise



Fig 8 Site of electrode in experiment 4 fig 7 Hepatoma moderately good tumour with many small capillaries but some polymorphs present which indicate that some degeneration has taken place H and E × 100

of tumour oxygen tension when oxygen was breathed was usually abolished Experiments were therefore performed to study the effect on tumour oxygen tension of inhalation of high pressure oxygen following injection of 5 HT

A typical experiment, in which tumour site A (hepatoma) showed a good rise of oxygen tension during the first period of high pressure oxygen inhalation is shown in Fig 9 After 5 HT 5 mg/kg I P there was no rise of tumour oxygen tension even when oxygen was inhaled at 5 atmospheres absolute After injection of the anti 5 HT anti histamine agent cyproheptadine 4 mg/kg I V, the response of tumour site A, to oxygen inhalation was nearly completely restored Injection of 5 HT did not diminish the rise of blood pressure due to the inhalation of oxygen under pressure The oxygen tension in the muscle was diminished by the 5 HT much more in this experiment than in the other experiments of this series

The experiment 43 in the rat (Fig 10) and experiment 54 in the mouse (Fig 11) are more typical in this respect and showed a profound effect of 5 HT on tumour oxygen tension with no effect on the oxygen tension of muscle

An interesting difference between the oxygen tension in tumour tissue (Jensen sarcoma) which failed to respond to the inhalation of oxygen under pressure after 5 HT and that of the muscle very near to the tumour, in which the response to oxygen inhalation is only slightly reduced by 5 HT is shown in Fig 10

Fig 9 Experiment 37 Rat with hepatoma From above downwards rectal temp —■— mean carotid blood pressure —▲—▲—▲—▲ muscle tumour A ——— tumour B — — and pressure of inhaled oxygen x—x 5-hydroxytryptamine in an amount of 5 mg/kg I P abolished the response of tumour A to oxygen inhalation and cyproheptadine 4 mg/kg I V largely restored the response Tumour B is an example of an electrode showing a negative response with pressure 5 HT abolished this and cyproheptadine partially restored the negative response

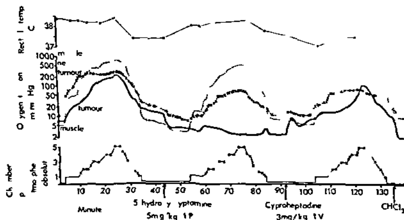



Fig 10 Experiment 43 Rat with Jensen sarcoma The tumour electrode ——— showed a 5 HT effect similar to tumour A fig 9 but muscle near tumour x x showed only a slight effect and the muscle in the other leg showed no 5 HT effect

In Fig 11 is illustrated the 5 HT effect in a spontaneous mammary carcinoma in the mouse but shows the difficulty which was experienced in the mouse in reversing the effect with the anti 5 HT, anti histamine agent cyproheptadine However after a second dose some response to oxygen inhalation was restored in the tumour This might be due to 5 HT causing such a marked stasis of blood in the tumour that the anti 5 HT agent cannot easily reach the zones affected

In Fig 12 the effect of cyproheptadine given before the 5 HT is illustrated and it will be seen that it partly prevented the 5 HT effect

3 *Direct pressure effects upon the tumour blood flow* Nine electrodes of the 77 in tumour showed a fall of oxygen tension during the inhalation of high pressure oxygen with the greatest depression usually occurring at the height of the pressure and a recovery of the oxygen tension when the pressure was reduced to atmospheric (see electrode tumour B in Fig 9) In general histological examination showed such electrodes to be near a zone of necrotic tumour This unexpected finding with 10 per cent of the electrodes cannot be dismissed as fortuitous A possible explanation of this rather surprising phenomenon is that necrotic zones of tumour may have cavities containing gas which is not in equilibrium with the blood and may therefore have been compressed when the chamber pressure was raised and caused deformation and vascular stasis in the adjacent area Examination of Fig 9 shows that electrode tumour B had this fall of oxygen tension during pressurisation abolished by 5 HT, but that it occurred again, somewhat diminished, after the cyproheptadine If as is suspected, 5 HT causes vascular stasis and capillary engorgement the behaviour of the electrode, tumour B in Fig 9, which was also observed in three other experiments would be consistent with the explanation offered

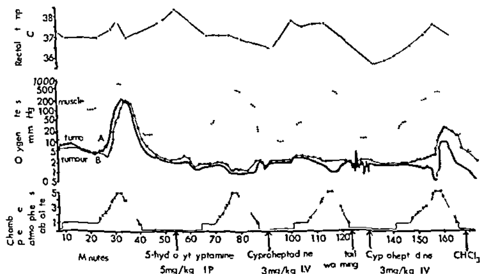
The possibility of oxygen inhalation under pressure actually reducing the oxygen tension in some zones of the tumour which are already relatively hypoxic has important radiotherapeutic implications

*Synkavit and inhalation of high pressure oxygen*

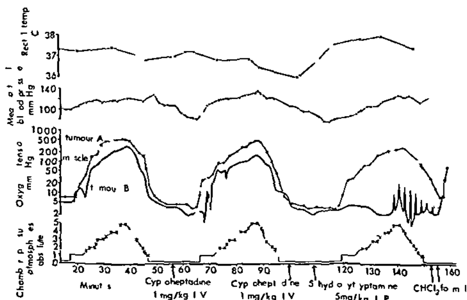
The effect of the radiosensitiser Synkavit on tumour oxygen tension during inhalation of high pressure oxygen was also investigated A typical experiment is shown in Fig 13 Two periods of inhalation of oxygen under increased pressure showed fairly consistent increases of oxygen tension in hepatoma and muscle and a third period after Synkavit 25 mg/kg I V indicated less response to the breathing of oxygen under pressure This was typical of this series of experiments which gave no evidence that Synkavit increased the oxygen response in tumour, a finding consistent with the hypothesis that radiosensitisation by Synkavit concerns some other mechanism

*Effect of inhalation of oxygen at high pressures on the oxygen tension of normal tissues*

In most experiments muscle was used as the control tissue, because it was desirable to avoid any procedure likely to shock the animal in view of the



F g 11 Experiment 54 Spontaneous mammary carcinoma n a C3H mouse Tumours A and B showed a marked 5 HT effect and two doses of cyproh ptad ne were needed before the re sponse to oxygen inhalat on was part ally restored The response of the muscle was not cl anged by 5 HT The temperature changed with oxygen inhalation in sp te of active steps to k ep the rectal tempe ature constant



F g 12 Exper ment 51 Rat w th l pat ma Cyprohepta l n did not alter the response to oxygen inhalation but prevented the 5 HT ffect on tumou A — — — and part ally pre vented t on tum our B ——— The ri e of tumour oxyg n ten on after death s due to ntra carotid inject on of formal n and s a useful ndicat on that the fixat has reached the electrode s te The blood pressu e changed with nhalation of oxygen

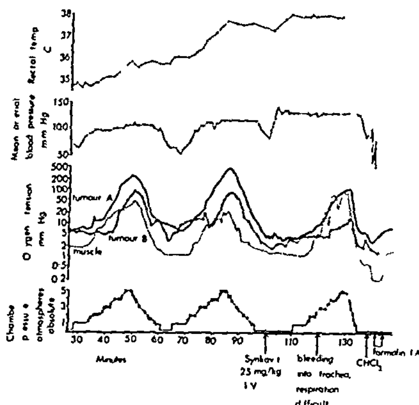



Fig 13 Experiment 40 Rat with hepatoma Two periods of high pressure oxygen inhalation gave similar responses and then Synkavit 25 mg kg I V was followed by rather reduced responses in tumour The formalin effect on tumour and muscle may be noted

effect of a fall of blood pressure upon tumour oxygen tension Muscle also has the advantage that there was rarely any trouble due to haemorrhage at the site of the electrode Records of the effect of inhalation of oxygen under pressure on the oxygen tension in muscle are shown in Figs 5, 7 9 10 11 12, 13, 14 The oxygen tension of muscle was usually such that fairly full radiosensitivity was present with the animal breathing air

In Fig 14, records of the oxygen tension in bone marrow and testis are also shown In the case of the testis the values indicate that an increase of radiosensitivity would have occurred during the inhalation of oxygen under pressure However too much weight must not be put on an isolated observation in an anaesthetised animal Measurements of the oxygen tension in brain were made in three experiments in which electrodes were inserted into brain and held rigidly in place by the stereotaxic instrument built into the pressure chamber (see Fig 1) The results showed that the oxygen tension in brain rose during the inhalation of oxygen under pressure, as would be expected but did not

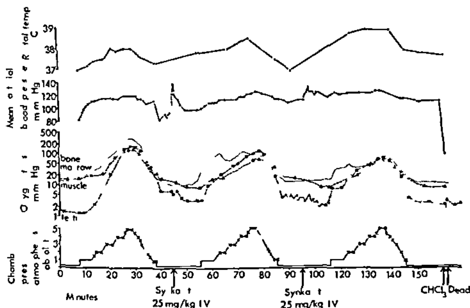



Fig 14 Experiment 47 Effect of high pressure oxygen inhalation on the oxygen tension of bone marrow ——△——△ muscle and testis — — — —□ Synkavit does not appear to have caused much change in the responses to oxygen

tend to diminish when the pressure remained constant at a high level However, the effect of inhalation of high pressure oxygen on the oxygen tension of various parts of the brain requires detailed investigation

*General effects of high pressure oxygen therapy*

The increase of mean systemic blood pressure which occurred in these anaesthetised rats and mice has already been mentioned (see Figs 9, 12 13 14) Other general systemic effects observed included a marked tendency for the animals to become hyperthermic during inhalation of high pressure oxygen This can be seen from the records of rectal temperature shown in Figs 5 7 and 9 to 14 These changes took place in spite of active steps to keep the rectal temperature constant including running cold water through the coil of copper pipe in the chamber Hyperthermia above 40 C combined with oxygen at 5 atmospheres absolute was rapidly fatal to rats Rats and mice anaesthetised with urethane tend to lose body temperature unless warmed it would thus appear that temperature regulation is impaired by urethane anaesthesia It was more difficult to keep the mice at a steady body temperature

In the early experiments a bag of soda lime was placed in the chamber to absorb $CO_2$ but the chamber was well ventilated because of small leaks and in the latter experiments the $CO_2$ absorber was omitted with no deleterious effects

Death during decompression occurred in some of the early experiments in spite of very slow increase of pressure and slow decompression In later experiments in which animals were tracheotomised because of carotid cannulation death during the experiment was much less frequent The presence of extensive zones of pneumonitis in animals dying during the experiment suggested respiratory obstruction It is possible that during decompression extensive congestion of the nasal mucosa and blockage of the trachea with mucus may have been a cause of pneumonitis and death Tracheotomy may have eliminated this hazard from the longer and more complicated experiments in the latter part of the series

## Discussion

The primary object of this investigation was to determine whether hypoxic zones in tumours with a radiosensitivity near to the nitrogen level could be raised to an oxygen tension of 10 mm Hg corresponding to a radiosensitivity about twice that of anoxic tissue by the breathing of oxygen at atmospheric pressure or whether the pressure chamber technique is necessary From the standpoint of radiotherapy the hypoxic zones in tumour are of great importance and it is interesting that over half the tumour zones investigated showed an oxygen tension of less than 4 mm Hg and would therefore be below the half way point of the increase of radiosensitivity obtainable by oxygen This is evidence in favour of the hypothesis that hypoxic zones in tumour are an important cause of tumour recurrence after radiotherapy Some of these hypoxic zones showed useful increases of radiosensitivity when the animals inhaled oxygen at atmospheric pressure, some did not while some showed useful increases of radiosensitivity during inhalation of oxygen under pressures of up to 3 atmospheres absolute Correlation with the histological appearances of the tumours at the sites of the electrodes suggested that many of these hypoxic tumour zones contained viable tumour cells and therefore at a first analysis high pressure oxygen inhalation during radiotherapy would reduce the recurrence rate

The detailed statistical analysis of these data involves the correlation of numerous variables including the three types of tumour and the histological grading of the electrode sites into 5 groups varying from good tumour to complete necrosis A full statistical analysis is being made with the aid of a digital computer and will be the subject of a separate communication The preliminary results indicate that, while some differences will be found between the three tumour types, these will be small compared with the differences between near necrotic and well vascularized zones in any one tumour type There is something to be gained from pooling the three types of tumour as it gives a better statistical sample from the clinical standpoint

The finding that the histological appearance of the electrode site is the most important factor determining the level of oxygen tension at that site was to be expected The finding that 9 out of 77 electrodes showed a fall of oxygen ten

sion during inhalation of high pressures of oxygen was unexpected but cannot be dismissed as an incidental finding or due to technical failure of the electrodes concerned Their behaviour was too consistent for this to be a reasonable explanation They were situated near necrotic zones and sometimes near macroscopic cavities which might well contain gas compressible during the increase of external pressure, with consequent deformation of the tumour and its capillaries This seems a possible explanation and the paradoxical effects of 5 HT injection on these electrodes is consistent with this hypothesis It is of course possible that the presence of the electrode might accentuate the effect of pressure deformation of the tumour but the general phenomenon, that when gas cavities are present in a tumour high external pressures may cause diminution of capillary circulation cannot be ignored and must be set in the balance against the beneficial effects of high pressure oxygen in radiotherapy

The importance of tumour blood flow in radiotherapy and chemotherapy cannot be emphasised sufficiently, and the factors which alter tumour blood flow will also affect tumour oxygen tension CATER et coll (1962b) found that tumour oxygen tension often varied directly with systemic blood pressure and was very susceptible to falls of blood pressure Therefore one good effect of inhalation of high pressure oxygen is the rise of blood pressure and some of the increase of the oxygen tension in tumour may be due to this GULLINO & GRANTHAM (1962) studied tumours transplanted into the ovary and found that adrenaline and acetyl choline affected tumour blood flow in the opposite sense to the changes produced in systemic blood pressure In their experiments the effect of hormones on the vessels of the long ovarian pedicle cannot be separated from their effect on the vessels in the tumour However there is evidence which suggests that the imperfectly innervated tumour vessels may be unduly sensitive to circulating adrenaline noradrenaline acetyl choline and 5 HT as CATER et coll also found that tumour oxygen tension was reduced by adrenaline and noradrenaline in spite of a rise of blood pressure and by 5 HT although the fall of blood pressure was small The rise of oxygen tension during oxygen inhalation is a good test of an adequate blood flow to tissues and it is noteworthy that 5 HT abolished this even with 5 atmospheres oxygen pressure Therefore 5 HT probably caused a profound slowing of tumour blood flow Under the conditions of the experiment the rise of oxygen tension in muscle is not usually altered and this discounts the suggestion that the oxygen is not reaching the arterial blood because of constriction of the bronchioles (VAN DEN BRENK 1962) The difficulty experienced in reversing the 5 HT effect with cyproheptadine in the mouse also suggests profound circulatory stasis in the tumour whereby the antidote may reach the affected vessels only with difficulty

High pressure oxygen inhalation will be advantageous in radiotherapy only if it increases the oxygen tension and thus radiosensitivity of the tumour while the radiosensitivity of the adjacent normal tissues remains essentially unchanged

The muscle showed marked rises of oxygen tension but was frequently above the critical level of oxygen tension with the animal breathing air. Our data on bone marrow, testis and brain are insufficient to merit discussion. HOWARD-FLANDERS & WRIGHT (1955) suggested that certain normal tissues, in particular bone and cartilage, might not be at maximum radiosensitivity when the patient was breathing air.

## Acknowledgements

We are indebted to Professor J. S. Mitchell for his constant encouragement and advice and *to Dr I. A. Silver of the Department of Veterinary Anatomy for many helpful discussions.* Dr D. D. Porteous of the Christie Hospital and Holt Radium Institute, Manchester, very *kindly* supplied us with tumour bearing mice. Two of us (Dr D. B. Cater and Mrs D. A. Watkinson) were supported by the British Empire Cancer Campaign, and one of us (Dr L. L. Schoeniger) by the American Cancer Society and Western Reserve University of Cleveland, Ohio. This financial support is most gratefully acknowledged.

## SUMMARY

Oxygen tension in rat and mouse tumours was measured by the oxygen-cathode technique and converted to radiosensitivity by the formula of GRAY (1961). Of 77 recordings made while the animals breathed oxygen at 5 atmospheres absolute in a specially constructed pressure chamber, 45 reached near maximum radiosensitivity and 9 showed a fall of oxygen tension. Reasons for this are discussed. Factors altering tumour blood flow are also important in radiotherapy. *After 5-HT, tumour oxygen tension failed to rise during oxygen inhalation even at* 5 atmospheres absolute.

## ZUSAMMENFASSUNG

In Tumoren von Ratten und Mausen wurde die Sauerstoffspannung mit der Sauerstoffkathodentechnik gemessen und mittels der Formel nach GRAY (1961) in Strahlenempfindlichkeit umgerechnet. Von 77 Messungen, die bei Sauerstoffatmung bei 5 absol. Atmospharen in einer spezialkonstruierten Druckkammer vorgenommen wurde, erreichten 45 nah zu maximale Strahlenempfindlichkeit wahrend 9 einen Abfall der Sauerstoffspannung zeigten. Die Ursachen hierzu werden besprochen. Faktoren, die die Tumordurchblutung andern, sind auch fur die Strahlentherapie wichtig. Nach 5 HT gelang es nicht selbst wahrend Inhalation bei 5 absol. Athmospharen, die Sauerstoffspannung im Tumor zu erhohen.

## RÉSUMÉ

La tension d'oxygene dans des tumeurs de rats et de souris a été mesurée par la technique de la cathode d'oxygène et a été convertie en radiosensibilité par la formule de GRAY (1961). Sur 77 mesures faites pendant que les animaux respiraient de l'oxygene à 5 atmosphéres absolues dans une chambre à pression construite spécialement, 45 atteignaient presque le maximum de radiosensibilité et 9 montraient une chute de la tension d'oxygène. Les raisons de ce phénomene sont étudiées. Les facteurs qui modifient le débit sanguin tumoral sont eux aussi importants en radiothérapie. Après 5 HT, la tension d'oxygene ne s'eleve pas pendant l'inhalation d'oxygène, même sous une pression de 5 atmosphères absolues.

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FROM THE PHYSICS DEPARTMENT OF THE NORTHERN IRELAND RADIOTHERAPY CENTRE BELFAST, NORTHERN IRELAND

# A WEDGE FILTER FOR COBALT 60 SUPPLEMENTATION OF CARCINOMA OF THE CERVIX UTERI PREVIOUSLY TREATED BY RADIUM

by

G R TAYLOR

The treatment of carcinoma of the cervix uteri by vaginal and intra uterine radium sources is frequently followed by the external application of gamma or roentgen ray fields to supplement the radium dosage in the parametria

A criticism of many techniques for such supplementation is that they raise a region of non uniform dosage to a higher level of dosage while still preserving the non uniformity of the dose This is particularly true for gamma or roentgen fields divided by a central lead strip and used in parallel anterior posterior opposition

The penumbra produced by the extended source of a cobalt unit when a simple rectangular lead block of suitable dimensions is placed centrally across the radiation field, may be used to attain some degree of matching of increasing cobalt and falling radium dosage However the relatively level peaks, particularly for large cobalt fields when combined with the still falling radium contribution produce a falling total dosage distribution The usefulness of the method is very limited and may only be used if one accepts a restricted plateau followed by a region of falling dosage which extends to the edge of the radiation field

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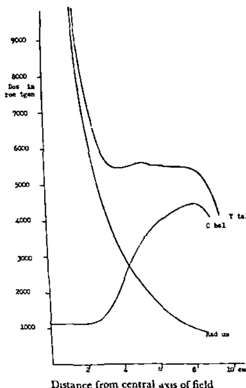



Fig 3 R d um cobalt and combined dosage dis t ibut ons at the m d l ne of a patient 20 cm thick for a field of 16 × 12 cm

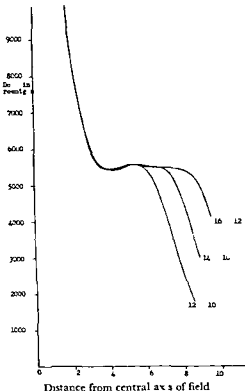



Fig 4 V ariat on of combined radium and cobalt distributions w th distance from the central axis of the field for var ous field sizes

The radium cobalt and combined dosage distributions at the mid plane of a patient 20 cm thick with the radium centrally placed are illustrated in Fig 3 The combined dosage distributions obtained for field sizes of 16 × 12 cm 14 × 10 cm and 12 × 10 cm when the cobalt treatment times are adjusted to give a plateau of 5 500 r are illustrated in Fig 4 On the same basis the combined distribution curve obtained for a 14 × 12 cm field was virtually coincident with that of a 14 × 10 cm field and is therefore not recorded Similar combined dosage distributions will apply for other thicknesses of patients as the isodose curves for this wedge maintain their cross field distribution sensibly constant over a range of depths

Direct addition of cobalt and radium doses was adopted to obtain the combined dosage distributions shown in Figs 3 and 4 It is however clear that as pointed out by TRANTER for the linear accelerator wedge it would be possible to adjust treatment times to achieve the same degree of matching if other assumptions are made as to the mode of summation of dose

## SUMMARY

A lead wedge filter is described which, when suitably placed in the radiation beam, ensures that the dose from the supplementary fields is a minimum at points already adequately irradiated by radium and thereafter increases laterally in such a way that it matches the falling radium dosage. A typical combined radium and cobalt dosage distribution is illustrated and the effect of variation in the cobalt field size considered.

## ZUSAMMENFASSUNG

Ein Bleikeilfilter wird beschrieben, das nach korrekter Anordnung im Strahlenkegel die Dose von den Hilffeldern an den Stellen, die bereits eine ausreichende Bestrahlung erhalten haben, auf ein Minimum reduziert und das lateral zunehmende Strahlung durchlässt entsprechend der dort abnehmenden Radiumstrahlung. Eine typische kombinierte Radium und Kobalt Bestrahlungsanordnung wird beschrieben und die Einwirkung von Feldgrössenveränderung der Kobaltstrahlung besprochen.

## RÉSUMÉ

Description d'un filtre cunéiforme en plomb qui, placé convenablement dans le faisceau de radiation, permet de délivrer aux points correctement irradiés par le radium une dose minimale par les champs complémentaires et de donner latéralement une dose croissante compensant la diminution de la dose curiethérapique. Les auteurs présentent un cas typique comme exemple de la distribution de dose combinée par le radium et le cobalt et étudient l'influence des variations des dimensions du champ de cobalthérapie.

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FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR ASSOC. PROF KURT LIDEN) AND RADIOTHERAPY (DIRECTOR ASSOC PROF MARTIN LINDGREN), UNIVERSITY OF LUND SWEDEN

# INDICATIONS AND METHODS FOR RADIOTHERAPY OF CAVERNOUS HAEMANGIOMAS

## A study of 1191 haemangiomas following radiotherapy

by

ULLA BRITA NORDBERG and JAN SUNDBERG

The role of radiation therapy in the treatment of haemangiomas is a subject of keen discussion Radiotherapy has been used very sparingly in England for example (LISTER 1938 WALTER 1953) because it has been felt that haemangiomas have a natural tendency to spontaneous healing In Germany on the other hand the opinion has been held that the risk of complications such as haemorrhage and infection is so great that a more active attitude is justified (MIESCHER 1944 WEISHAAR & KOSLOWSKI 1959) The Swedish author NOTTER (1956), recommended radiotherapy for haemangiomas in areas where there is an enhanced risk of these complications

The authors in the present communication examine

1 The results one year following the radiation treatment of haemangiomas and the extent to which these results were affected by such factors as the size of the growths the quality of radiation used and the dose administered

2 The effect these same original factors had on the appearances of the skin 5 to 15 years following therapy and whether radiotherapy can be shown to have had any injurious effects

Submitted for publication 11 October 1962

**Table 1**

*Distribution in per cent in the different age group (all patients)*

| Year of treatment | Number of patients | Age in years 0—½ | ½—1 | 1—2 | 2—10 |
|---|---|---|---|---|---|
| 1945 | 130 | 46 | 33 | 16 | 5 |
| 1950 | 274 | 47 | 31 | 20 | 2 |
| 1955 | 426 | 64 | 26 | 8 | 2 |
| Total | 830 | 56 | 29 | 13 | 2 |

Haemangiomas are usually classified in the medical literature according to their histologic appearances into the following categories haemangioma capillare, haemangioma simplex haemangioma cavernosum and haemangioma racemosum This classification, however is unsuitable for clinical use and at Jubileumskliniken in Lund haemangioma simplex and haemangioma cavernosum are classified on a clinical basis into surface (cutaneous) and deep (subcutaneous) types, two types that commonly occur simultaneously in one haemangioma The present writers will not discuss haemangioma racemosum and those types of haemangioma capillare known as haemangioma vinosum and angioma stellatum

## Material

This investigation, which was carried out in 1961, includes all haemangiomas in children under 10 years of age who were given radiotherapy in the years 1945, 1950 and 1955 The number of patients in those years was 130 274 and 426 respectively, and the number of haemangiomas 169, 402 and 620 respectively a total of 830 patients with 1 191 haemangiomas of these haemangiomas 868 (72 %) had only superficial components, 311 (27 %) both superficial and deep elements and 12 (1 %) only deep components

The size of the haemangiomas showed wide variations Haemangiomas having a maximum measurement of 15 mm in any direction are called minor there are 756 minor and 435 major haemangiomas in this investigation The haemangioma was single in 598 patients, and 232 patients had multiple haemangiomas The number of haemangiomas per patient in this latter group varied from 2 to 50, the usual number being 2 to 4 The distribution between the sexes is the same as that given in the literature, namely one male to two females

Table 1 gives the age at the time of the first treatment The aim has been to treat haemangiomas as early as possible, preferably during the first year of life The table also shows that the number of patients over the age of one year has diminished with the passage of time, falling from 22 % to 10 % of the total number between 1950 and 1955

## Investigation and percentage of answers

All patients who were not re examined in 1961, were asked to fill in a questionnaire giving

1 Details of the present appearances of the skin, any changes in the skin in the form of atrophy pigmentation de pigmentation telangiectases, or other abnormality

2 To state in brief whether or not the result was cosmetically satisfactory

3 To state whether they were healthy and normally developed

Certain special problems, however e g indications and counter indications for radium therapy and the possible occurrence of disturbances in growth due to irradiation of epiphyses, made it necessary for a number of patients to come to the clinic for re examination This examination comprised inspection and palpation with assessment of any permanent changes in the skin and any deformity or hypoplasia in the surrounding tissue Most of the patients also had routine haematologic studies including haemoglobin and red, white and differential blood counts The blood tests were all within normal limits Further investigations such as roentgenography or ophthalmoscopy were carried out where there was reason to suspect that the dose to any one organ was excessive

One hundred and thirty five patients with 178 haemangiomas were requested to come to the clinic, and 695 patients with 1 013 haemangiomas were invited to fill in a questionnaire, some of this latter group elected to come to the clinic for re examination instead Thus a total of 267 patients with 354 haemangiomas (30 % of the total number) were re examined at the clinic and 492 patients with 733 haemangiomas (62 %) filled in the questionnaire This provided data on long term results for 759 patients with 1 087 haemangiomas (92 %) Similar data are not available for 71 patients with 104 haemangiomas (8 %) Some of these latter patients had died but the majority had moved to other districts and could not be traced even by consulting parish registries For 64 of these patients with 96 haemangiomas only a one year control examination is recorded, but not even this is available for 7 patients with 8 haemangiomas

## Principles of treatment

Haemangiomas were treated at Jubileumskliniken during the period covered by the investigation with radium radium combined with contact roentgen therapy or by contact roentgen therapy alone A few patients received roentgen therapy, generally tangentially

The principle followed was that haemangiomas in especially radiosensitive areas, e g epiphyses and undeveloped breasts were given contact roentgen therapy The method of treatment was otherwise determined by the depth of the haemangioma and by its spread at the surface Minor superficial haemangiomas received contact roentgen therapy (50 kV, 0 5 mm Al additional

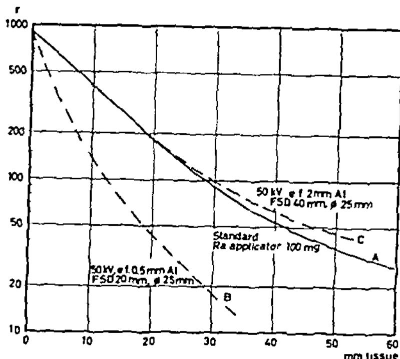



Fig 1 Central axis depth dose distribution for radium and roentgen contact therapy Surface dose 900 r

filter 20 mm FSD corresponding to a HVL of 3 mm soft tissue) Contact roentgen therapy was also often given to major haemangiomas including some where the changes extended down beneath the superficial layers of the skin The haemangiomas were then compressed during treatment and in some cases the quality of the rays was modified (50 kV 0 5 to 1 mm Al additional filter 40 mm FSD corresponding to a HVL of about 4 to 6 mm soft tissue) Many haemangiomas with relatively thick superficial components were given radium therapy Haemangiomas with subcutaneous components were mostly treated with radium or in isolated instances with tangential roentgen therapy Those haemangiomas that showed substantial regression after radium treatment but still had a minor superficial residue were usually given final treatment with contact roentgen therapy Isolated cases were recommended for surgical therapy if any disfiguring haemangioma residue following radiotherapy existed

The first radium treatment consisted of a dose of 700 to 800 r at a depth of about 3 mm corresponding to 900 to 1 000 r on the skin surface following the method described by STRANDQUIST (1939) (Fig 1) The radium dose for each additional application for those haemangiomas that received several treatments was usually 500 to 700 r at a depth of 3 mm The surface dose in

**Table 2a**

*Results of treatment in per cent for all re-examined haemangiomas*

| Total number | After one year | | | After 5—15 years | |
|---|---|---|---|---|---|
| | Disappeared | Almost disappeared | Regression | Disappeared | To surgical therapy |
| 1 087 | 44 | 35 | 21 | 99 | 1 |

**Table 2b**

*Result of treatment in per cent for all re-examined haemangiomas comparison between haemangiomas without and with deep components major and minor haemangiomas and haemangiomas in males and females*

| | Number of haemangiomas | Skin after 5 to 15 years | | |
|---|---|---|---|---|
| | | No changes | Minor changes | Major changes |
| All haemangiomas | 1 087 | 47 | 48 | 5 |
| Haemangiomas with only surface components | 794 | 47 | 49 | 4 |
| Haemangiomas with deep components | 293 | 42 | 51 | 7 |
| Size of haemangiomas $\leq$ 15 mm | 685 | 54 | 43 | 3 |
| $>$ 15 mm | 402 | 37 | 53 | 10 |
| Males | 357 | 49 | 46 | 5 |
| Females | 730 | 47 | 48 | 5 |

contact roentgen therapy was usually 1 000 r for the first treatment and 600 to 800 r for subsequent treatments

The majority of haemangiomas were treated by one of three methods (routine radiation treatment)

1 Radium treatment alone (one or two applications)

2 One radium application followed by one contact roentgen therapy treatment

3 Contact roentgen therapy alone (one or two treatments)

A minority of growths were treated by other methods (non routine treatment) Some of these were given radium treatment or contact roentgen therapy three times A number received one or more radium applications combined with one or more contact roentgen therapy treatments the first treatment consisting alternately of radium and contact roentgen therapy A few haemangiomas received roentgen therapy generally tangential The interval between the treatments was generally about 180 days occasionally about 120 days and rarely more than 200 days

An examination of the percentage distribution between the different types of treatment described above reveals that 53 % of the haemangiomas received some kind of radium treatment on at least one occasion whereas 45 % were

**Table 3**

*Result of treatment in per cent for different age groups (routinely treated haemangiomas)*

| Age in years | Number of haemangiomas | Haemangioma after one year: Disappeared | Almost disappeared | Regression | Skin after 5 to 15 years: No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|---|
| 0—1/2 | 530 | 49 | 38 | 13 | 45 | 51 | 4 |
| 1/2—1 | 273 | 47 | 39 | 14 | 51 | 47 | 2 |
| 1—2 | 128 | 56 | 30 | 14 | 47 | 49 | 4 |
| 2—10 | 21 | 31 | 49 | 20 | 62 | 26 | 12 |
| Total | 952 | 50 | 36 | 14 | 50 | 47 | 3 |

given contact roentgen therapy only and 2 % received roentgen treatment. The number of patients receiving radium therapy has gradually declined during the latter part of the 1950 s (NORDBERG 1961) and the number treated with contact roentgen therapy has increased. Treatment to day is mostly by contact roentgen therapy.

Since many patients had more than one haemangioma and since the therapeutic technique and the results obtained vary for different haemangiomas on the same patient, the percentage figures cited above, and the figures in all the following tables refer to the number of haemangiomas and not to the number of patients.

## Results

*One year results.* All the haemangiomas that were re-examined have been assigned to one of three groups with the assistance of the case notes (Table 2a). The first group ("disappeared") consists of haemangiomas that had completely disappeared, the second ("almost disappeared") contains those in which only minor haemangioma residues were discernible; the third group ("regression") contains those that had receded to a greater or lesser degree but not completely. This last group also includes the 12 cases (1 % of the material) that were later referred for surgical therapy. The percentage distribution within the three groups specified in the 96 haemangiomas in which only the one-year results are known is 41, 30 and 29 % respectively.

*Long term results.* As there is no haemangioma residue remaining after 5 to 15 years, the long term assessment applies to the appearance of the skin, i.e. the long term results from the cosmetic point of view. The first group ("no changes") contains those cases in which the skin was completely normal; the second ("minor changes") contains those in which the skin showed isolated telangiectases, slight pigmentation or de-pigmentation. The cosmetic results in both these groups were satisfactory. There were more obvious changes in the skin in the third group ("major changes").

Data on the long term results for 1 087 haemangiomas, 952 of which re-

**Table 4**

*Result of treatment in per cent after different treatments and different doses (routinely treated haemangiomas)*

**Table 4a — one treatment**

| Treatment | Surface dose in r | Number of haemangiomas | Haemangioma after one year: Disappeared | Almost disappeared | Regression | Skin after 5 to 15 years: No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|---|---|
| Radium | ≤ 900 | 56 | 47 | 41 | 12 | 57 | 38 | 5 |
| | > 900 | 99 | 61 | 30 | 9 | 66 | 31 | 3 |
| Roentgen contact therapy | ≤ 900 | 46 | 68 | 24 | 8 | 74 | 24 | 2 |
| | > 900 | 262 | 74 | 24 | 2 | 51 | 47 | 2 |

**Table 4b — two treatments**

| Treatment | Surface dose in r at the 1st treatment | Number of haemangiomas | Haemangioma after one year: Disappeared | Almost disappeared | Regression | Skin after 5 to 15 years: No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|---|---|
| Radium | ≤ 900 | 66 | 32 | 31 | 37 | 41 | 55 | 4 |
| | > 900 | 97 | 36 | 40 | 24 | 49 | 46 | 5 |
| Roentgen contact therapy | ≤ 900 | 34 | 40 | 43 | 17 | 59 | 38 | 3 |
| | > 900 | 147 | 31 | 50 | 19 | 35 | 62 | 3 |
| Radium + roentgen contact therapy | ≤ 900 | 87 | 30 | 53 | 17 | 40 | 57 | 3 |
| | > 900 | 58 | 37 | 52 | 11 | 55 | 43 | 2 |

ceived routine radiation treatment are available A survey of the long term results for all the radiotherapeutically treated haemangiomas that were re examined irrespective of the type of treatment they had received is given in Table 2b Haemangiomas with subcutaneous components are also placed in this table in juxtaposition to those without such components for comparison Both the one year results and the long term results are considerably worse for the subcutaneous category There is also as can be seen from Table 2b, a marked difference between major and minor haemangiomas both in the one year and long term results There is no difference between the results for males and those for females

The results for haemangiomas that received routine radiation treatment are better than those for the total number of haemangiomas irrespective of the type of treatment This may be explained by two factors

1 The majority of the haemangiomas receiving non routine treatment were given three or four treatments and thus received larger skin doses than

**Table 5**

*Result of treatment in per cent after different treatments and different sizes of haemangiomas (routinely treated haemangiomas)*

**Table 5a — one treatment**

| Treatment | Size of haemangiomas in mm | Number of haemangiomas | Haemangioma after one year: Disappeared | Almost disappeared | Regression | Skin after 5 to 15 years: No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|---|---|
| Radium | ≤ 15 | 102 | 63 | 31 | 6 | 70 | 28 | 2 |
| | > 15 | 53 | 44 | 39 | 17 | 47 | 45 | 8 |
| Roentgen contact therapy | ≤ 15 | 252 | 74 | 23 | 3 | 56 | 42 | [illegible] |
| | > 15 | 56 | 68 | 30 | 2 | 47 | 50 | 3 |

**Table 5b — two treatments**

| Treatment | Size of haemangiomas in mm | Number of haemangiomas | Haemangioma after one year: Disappeared | Almost disappeared | Regression | Skin after 5 to 15 years: No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|---|---|
| Radium | ≤ 15 | 84 | 50 | 33 | 17 | 50 | 47 | 3 |
| | 15 | 79 | 18 | 39 | 43 | 42 | 52 | 6 |
| Roentgen *contact* therapy | ≤ 15 | 116 | 40 | 43 | 17 | 43 | 55 | 2 |
| | > 15 | 65 | 22 | 56 | 22 | 34 | 62 | 4 |
| Radium + roentgen contact therapy | ≤ 15 | 80 | 38 | 53 | 9 | 54 | 45 | 1 |
| | > 15 | 65 | 27 | 52 | 21 | 37 | 58 | 5 |

those treated in the normal manner. A greater number of skin changes due to radiation may therefore be expected in this group.

2. When haemangiomas that had received non-routine treatment, i.e. 12 % of the total material, are excluded the cutaneous group diminishes by 9 % and the subcutaneous group by 22 %, minor haemangiomas by 7 % and major ones by 21 %. It is therefore evident that major haemangiomas and haemangiomas with subcutaneous components are over-represented in the non-routine groups. These types of haemangiomas give a less satisfactory cosmetic result than minor haemangiomas and haemangiomas with only cutaneous components.

The non-routine treated haemangiomas form a non-homogenous group as far as the therapeutic technique is concerned. There are also relatively few of them compared with those that had routine radiation treatment. With due consideration to these factors it was therefore thought correct to omit non

Table 6

*Comparison between the one year result and the long term result in per cent for different sizes of haemangiomas (routinely treated haemangiomas)*

| Number of haemangiomas | Size of haemangiomas in mm | Haemangioma After one year | Haemangioma After 5 to 15 years | Skin after 5 to 15 years No changes | Minor changes | Major changes |
|---|---|---|---|---|---|---|
| 323 | ≤ 15 | Disappeared | Disappeared | 57 | 41 | 2 |
| 153 | > 15 | » | » | 31 | 67 | 2 |
| 206 | ≤ 15 | Almost dis- | » | 62 | 37 | 1 |
| 146 | > 15 | appeared | » | 37 | 60 | 3 |
| 54 | ≤ 15 | Regression | » | 52 | 39 | 9 |
| 70 | > 15 | » | » | 36 | 44 | 20 |

routine treated haemangiomas in further tables Tables 3 4 5 and 6 thus contain only those haemangiomas that received routine radiation treatment

The results for different age groups may be seen in Table 3 The number of haemangiomas in the 2 to 10 age group is so small that the less satisfactory results in this group are not necessarily significant There is otherwise no marked difference between the different age groups

Tables 4a and 4b show the extent to which the results of the treatment are influenced by the size of the dose Cases that received two treatments (Table 4b) are grouped according to the size of the first surface dose The boundary between a low and a high dose has been fixed at 900 r Corresponding depth doses for a normal radium application (A) and contact roentgen irradiation of normal quality (B) are shown in Fig 1

Despite the fact that the number of haemangiomas in some groups is rather small the tables show that for radium treated haemangiomas both the one year results and the long term results are better when the higher dose was given For haemangiomas that received contact roentgen therapy the long term results are better for those given the lower dose

The haemangiomas are divided according to size in Tables 5a and 5b the boundary between the major and minor haemangiomas being fixed at 15 mm as described above The results of the different types of treatment when given once (Table 5a) or twice (Table 5b) are compared within these two main groups The results for the major haemangiomas are less satisfactory those for the different kinds of treatment are basically the same as those shown in Tables 4a and 4b

The possible variation in the results with the site of the haemangioma was also investigated Haemangiomas were divided into three main groups those situated on the head the trunk and the extremities The one year results are about the same in all three groups and are similar to the results for all routine

## Table 7

*Supplementary examinations — Doses and fractionation time for irradiation of the skeleton, lens and thyroid gland*

### Table 7a — Irradiation of the skeleton

| Patient's No | Area examined | Dose in rad at the examined part of the skeleton at treatment 1 | 2 | 3 | Interval in months between treatments 1—2 | 2—3 | Total dose in rad | Total fractionation time in months |
|---|---|---|---|---|---|---|---|---|
| 44 18 24 | Thoracic vertebras | 600 | 500 | 400 | 6 | 8 | 1 500 | 14 |
| 44 10 13 | Cervical vertebras | 900 | | | | | 900 | |
| 45 01 18 | Wrist | 600 | 600 | | 5 | | 1 200 | 5 |
| | Skull | 600 | | | | | 600 | |
| 55 05 03 | Femur | 70 | 90 | | 6 | | 160 | 6 |
| 50 06 20 | Skull | 700 | 700 | 400 | 8 | 9 | 1 800 | 17 |
| 49 10 05 | Shank | 130 | 90 | | 8 | | 220 | 8 |
| 49 02 06 | Thoracic vertebras | 600 | | | | | 600 | |
| 49 06 27 | Shoulder | 200 | | | | | 200 | |
| 49 08 23 | » | 70 | 70 | 70 | 4 | 6 | 210 | 10 |
| 50 06 19 | Skull | 800 | 500 | | 4 | | 1 300 | 4 |
| 49 10 22 | » | 800 | 600 | | 4 | | 1 400 | 4 |

### Table 7b — Irradiation of the lens

| Patient's No | Dose in rad at treatment 1 | 2 | Total dose in rad | Total fractionation time in months |
|---|---|---|---|---|
| 50 06 19 | 90 | 60 | 150 | 4 |
| 49 10 22 | 140 | 110 | 250 | 4 |
| 49 12 18 | 120 | 100 | 220 | 4 |
| 49 03 21 | 100 | 100 | 200 | 4 |

### Table 7c — Irradiation of the thyroid gland

| Patient's No | Dose in rad at treatment 1 | 2 | Total dose in rad | Total fractionation time in months |
|---|---|---|---|---|
| 45 01 27 | 90 | 60 | 150 | 5 |
| 49 09 23 | 140 | 100 | 240 | 4 |
| 55 09 03 | 300 | 75 | 375 | 10 |

radiation treated haemangiomas shown in Table 3. The long term results are better for haemangiomas situated on the head. Of these latter 68 % showed no skin changes after 5 to 15 years and 29 % showed only minor changes. The corresponding figures for the other two groups are 40 % and 42 % respectively without changes and 56 % and 54 % respectively with minor changes. A

**Table 8**

*Three cases with multiple haemangiomas doses and fractionation periods*

| Patient's No | Number of haemangiomas | Interval between treatments | Active bone marrow | Dose in rad on Thyroid gland | Gonads | Lens |
|---|---|---|---|---|---|---|
| 55 03 18 | 5 | | 9 | 20 | 5 | 70 |
| | | 3 months | 1 | 0 | 0 | 0 |
| Total | | 3 months | 10 | 20 | 5 | 70 |
| 50 04 14 | 15 | | 20 | | 25 | |
| | | 8 days | 20 | | 25 | |
| | | 4 months | 15 | | 40 | |
| | | 4 months | 15 | | 25 | |
| Total | | 8 months | 70 | < 20 | 115 | < 10 |
| 50 02 13 | 18 | | 20 | 80 | 3 | 60 |
| | | 1 day | 10 | 80 | 9 | 20 |
| | | 4 months | 10 | 20 | 12 | 20 |
| | | 4 months | 1 | 10 | 0 | 20 |
| Total | | 8 months | 41 | 190 | 24 | 120 |

relatively larger number of the haemangiomas located about the head were minor ones This may be one explanation of the fact that the long term results are better for this group than for the other two groups Another explanation is that the vascularization and thus also the nutrition of the skin is better in the head than in the rest of the body There is consequently better healing of the skin changes in this region brought about mechanically by haemangiomas and those caused by radiation

The material was still further divided by specifying the sites even more closely e g upper and lower halves of the face and scalp or chest back and abdomen The results are essentially the same as that noted for the principal groups within these subdivisions Such deviations as could be noted are explained by the fact that the number of haemangiomas is small for certain groups

The relationship between the one year results and the long term results are illustrated in Table 6 No single case with a haemangioma residue was found at control examination after 5 to 15 years (Table 2a although other skin changes that were to a greater or lesser degree disfiguring were often evident The haemangiomas are divided in the table according to size and one year results The results after 5 to 15 years are given for each group and are similar for all haemangiomas except for the group containing those large haeman-

giomas that after a year showed only regression. The long term results in this group were often unsatisfactory but for the other haemangiomas the long term results did not differ considerably from the average result. As less satisfactory long term results may be expected for those major haemangiomas that show only regression after one year there is good reason to refer these patients while still in childhood for plastic surgery in order that supplementary non radiotherapeutic treatment may be given at a suitable opportunity.

*Supplementary investigations where complications due to radiation are probable.* There are numerous accounts in the literature of injuries arising from radiotherapy applied to haemangiomas. These injuries usually occur in patients who have been given doses far above those regarded as permissible at our clinic.

Table 7 deals with a number of patients in whom supplementary investigations in connection with their re examination were performed. The table shows the dose at each treatment, the interval between the treatments and the total dose. The doses are given in rads to make it possible to add doses of differing quality.

*The radio sensitivity of epiphyses*, i. e. the lowest dose at which the risk of growth disturbances or other damage to epiphyses arises, has often been discussed (MAU 1953, FISCHER 1955, WEISHAAR & KOSLOWSKI 1959, BONSE & GRAF 1960). It is generally stated, without any precise information on the quality of the radiation being given, that the risk of any permanent growth disturbances is slight after a maximum tissue dose of 300 r during one treatment. WEISHAAR & KOSLOWSKI stated that tolerance increases with fractionation and diminishes with harder radiation. These two writers believed that the tolerance limit stated is also applicable to contact roentgen therapy. A tissue dose of $> 400$ r produces a risk of the development of deformities.

Twelve patients among those who came to the clinic for re examination and in whom the tissue dose in some part of the skeleton was high, were subjected to roentgen examination for the detection of possible skeletal changes caused by radiation. It was not possible to demonstrate any deformities or damage to the skeleton even though the dose at a single treatment was as high as 900 rad and the total dose reached 1 800 rad over a 17 month period (Table 7a).

The danger of causing a *radiation cataract* when treating haemangiomas near the eye was discussed by e. g. MERRIAM & FOCHT (1957), QUIST & ZACHAU CHRISTIANSEN (1959) and BEK & ZAHN (1960). A single dose of about 200 rad gamma radiation to the lens is considered to be dangerous. The longer the fractionation period the greater the tolerance and thus the limit of tolerance is considered to be 550 rad fractionated over a period of three months. Four patients were examined by an ophthalmologist. The lens had been given a total dose varying between 150 rad and 250 rad with a

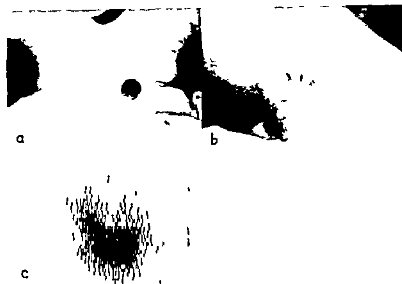



Fig 2 a) Appearances of haemangioma before radiotherapy b) State of skin at control-examination with (c) scintigram and radioiodine tracer tests dose administered 7.5 μC thyroid uptake 2 hrs 23 thyroid uptake 24 hrs 42 urine excretion 0—24 hrs 33

fractionation period of 4 months (Table 7b) There were no signs of radiation cataract in any instance

There appears to be no reference in the literature to *the radiosensitivity of the thyroid gland* in children The general opinion is however that this organ is relatively insensitive Three patients of the present series were examined by means of radio iodine tracer tests and scintigrams The tissue dose in the thyroid gland was estimated at 150 240 and 375 rad respectively (Table 7c) The tracer studies in all three patients were within normal limits Using these methods of detection a dose of 375 rad apparently caused no changes in the thyroid gland The appearances before treatment from a case of this type are shown in Fig 2 including the present state the scintigram and the radioiodine test

Hypoplasia or aplasia of the female breast after radiation treatment in childhood has been reported in a few papers (RUBE 1954 GREGL & WEISS 1962 inter alia) The authors agree on the high *radiosensitivity of the breast anlage* but no definite information is yet available on the tolerance limit Among 27 females in whom the haemangiomas were situated near a mammilla two presented evidence of slight mammary hypoplasia The appearances of one of these haemangiomas before treatment and in its present state is shown in Fig 3 The doses to the breast tissue in these two patients could be estimated at 580 and 1 150 rad respectively given in one treatment and in two treatments with an interval of 4 months respectively

There is no definite indication for early treatment of haemangioma situated in other parts of the body.

Contact roentgen therapy appears to be superior to radium therapy from both the theoretical and the practical points of view. Radium therapy implies total body irradiation for both patient and staff and ought therefore to be avoided (NORDBERG 1961). Contact roentgen therapy is easier to apply. The duration of the treatment is a matter of seconds, during which time the child and the roentgen tube can be fixed in relation to each other so that the field of treatment is strictly defined. If the extent of the beam is strictly limited, the total irradiation is kept at a minimum for both patient and staff.

Practically all haemangiomas that receive radiotherapy should therefore be given contact roentgen therapy. The majority of haemangiomas with subcutaneous extensions may also be treated successfully by compression of the haemangioma and, if necessary, modification of the quality of the rays to, for example, 50 kV, 2 mm Al additional filter, FSD 40 mm. This quality has a HVL that is about that of 8 mm soft tissue and has, as is shown in Fig. 1, a depth dose distribution that practically corresponds to that of a normal radium applicator. Fifty-eight haemangiomas with subcutaneous components in the present material were given contact roentgen therapy and 136 haemangiomas of this type received radium therapy. After one year 43 % and 40 %, respectively, had disappeared completely and 26 % and 24 %, respectively, were incompletely cured, whereas at the time of the control examination 40 % and 47 %, respectively, showed no changes in the skin and 3 % and 7 %, respectively, were cosmetically unsatisfactory. It is only very seldom therefore that radium therapy is indicated. A few haemangiomas with large deep components may require roentgen treatment which should, if possible, be tangential.

The surface dose at the first treatment should be 800 to 900 r for contact roentgen therapy. WALTER (1953) has shown that a lesser dose gives worse one year results. A dose of 400 r gives only 9 % healing compared with 45 % for a dose of 800 r. A higher dose, of say 1 000 to 1 500 r, may produce more rapid healing but at the same time the cosmetic result will be worse (HULTBERG 1943 and WALTER 1953 inter alios), there will be an increase in pigmentation, depigmentation and atrophy of the skin. The frequency of haemangiomas that showed no skin changes whatsoever at reexamination in the present material was three times greater when the surface dose during treatment was $\leq 900$ r than when the dose was $> 900$ r (Tables 4a and 4b).

## Conclusions

1. Radiotherapy is not generally indicated for the treatment of haemangiomas.

2. Rapidly growing haemangiomas on the face should be treated early

for functional, psychologic and cosmetic reasons Haemangiomas in the perineum and adjoining regions should also be treated early because of the risk of infection and ulceration

3 Haemangiomas should be treated in principle with contact roentgen therapy of a quality adjusted to the deepest component of the haemangioma, a HVL corresponding to 3 to 8 mm soft tissue

4 The suitable surface dose for the first treatment is 800 to 900 r

## SUMMARY

The results of radiation treatment of 1191 haemangiomas in 830 patients have been re examined with special reference to changes in the appearances of the lesion one year later the appearances of the skin 5 to 15 years following therapy and the possibility of injurious effects from the treatment

## ZUSAMMENFASSUNG

Eine Untersuchung der Resultate nach radiologischer B handlung von 1191 Hаman giomen b i 830 Patienten wurde ausgeführt Spezielles Interesse wurde folgende Faktoren gewidmet das Aussehen des Hamangioms ein Jahr nach der Behandlung das Aussehen der Haut 5 bis 15 Jahre nach der Behandlung und die Moglichkeit von schadlichen Wirkungen der Behandlung

## RÉSUME

Les auteurs ont ré examine les résultats du traitement par les radiations de 1191 héman giome chez 830 malades ils ont particulièrement étudié les modifications de l aspect de la lésion au bout d un an l aspect de la peau 5 a 15 ans apres le traitement et la possibilité de lésions dues au traitement

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Most data obtained to date pertaining to these effects have been derived from acute exposure to high doses of radiation. Moreover, until recently almost all experimental work was carried out with roentgen rays whose energy spectra differ from those emitted by the principal radioisotopes. From these studies the conclusions arrived at are often irrelevant to the problem of low dose rate chronic irradiation, and are thus misleading.

It is therefore essential to design irradiation facilities with these specific problems in mind.

*Characteristics of facilities for chronic irradiation.* The facility should be able to deliver a fairly wide range of dose rates. Both long continuous irradiations (several weeks), and accurately timed short exposures (a few minutes), should be attainable. Large target volumes are also required.

Very large units installed in specially designed buildings or restricted areas are very useful, but there is ample justification for an apparatus that can be used in a pre-existing room of normal size and construction, with minimum additional shielding.

Finally, the conditions of irradiation should be reproducible at intervals of several months or even years.

Comparable basic principles found in all existing facilities are as follows:

1. Use of moderate quantities of monochromatic high specific activity gamma emitters with long half-life, e.g. $^{60}$Co and $^{137}$Cs (DESAIVE et coll. 1957);
2. Large radiation field volume relative to the target size;
3. Target in normal environmental conditions during long exposures.

These facilities can be broken down into three broad categories:

I. *Self contained*, i.e. target is placed within the confines of the facility.
e.g. gammacell 220 containing 16 000 curies $^{60}$Co produced by Atomic Energy of Canada, Ottawa; 6 curies $^{60}$Co and 5 curies $^{137}$Cs irradiators at the Physics Department, Institute of Cancer Research, Royal Cancer Hospital, London (QUASTLER et coll. 1959).

II. *Transportable external beam*, i.e. source is only shielded in one position in the storage container at which time it is transportable.
e.g. 4 000 curies $^{60}$Co irradiator at Cornell University, N.Y., U.S.A.; 215 curies $^{137}$Cs irradiator at the Department of Agriculture, Harrow, Ontario; 50 curies $^{60}$Co irradiator at the Banting and Best Institute of Medical Research, University of Toronto.
(The unit described in this article also falls into this category.)

III. *Fixed external beam*, i.e. source is stored in a permanent location when in the safe position.
e.g. 8 curie $^{60}$Co irradiator at Division of Biological and Medical Research,

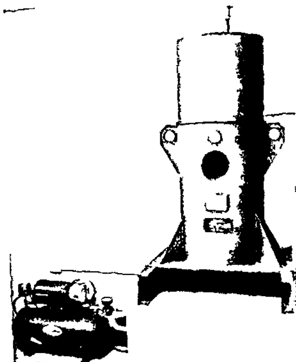


Fig 1 Overall picture of the unit

Argonne National Laboratory, Argonne Illinois U S A (SACHER et coll 1955) 1 340 curies $^{60}$Co irradiator at the Texas Engineering Experimental Station College Station Texas U S A (RANDALL 1958)

*Technical description* The irradiation facility herein described is a low dose rate transportable external beam unit designed and constructed by the Commercial Products Division of Atomic Energy of Canada Ltd It was installed at the Faculty of Medicine of Laval University Quebec and loaded on November 28th 1961 with 73 6 curies of cobalt 60 (Fig 1)

The source itself comprises 1 mm diameter by 1 mm long nickel plated cobalt 60 pellets having an initial specific activity of approximately 163 5 curies/g

These pellets are sealed by welding into a stainless steel capsule which in turn is welded into a second capsule of the same material thereby giving a double seal and ensuring maximum protection against contamination

The sealed source is mounted in a lead filled steel encased drawer and is held in position by a truarc ring (Fig 2)

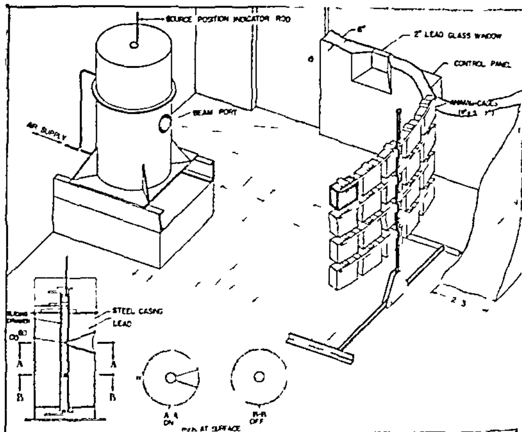



Fig 2 Outline of unit and room showing surface radiation fields

The drawer which has a teflon seal at either end slides vertically in the central bore tube of a cylindrical storage container which is also comprised of lead encased in steel 1/4 (6 4 mm) thick (Steel encasement provides protection against fire hazard )

When the drawer is at the bottom of its travel in the bore tube, the source is completely surrounded by a minimum of 7 5 inches (19 cm) of lead The external fields at the surface are shown in Fig 2 In this position the unit can be used as its own shipping container The total weight of the unit is 2 400 lbs (approx 1 100 kg)

When the drawer is in the upper position the source stops directly opposite a 38 conical port allowing a collimated beam of radiation to be projected into the shielded room

The drawer movement is achieved by the application of air pressure at either end The operating pressure of 25 psi is supplied by a small compressor

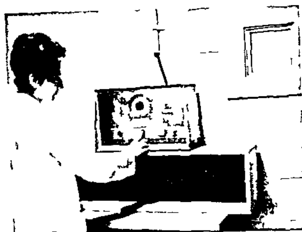


Fig 3 Control console and lead glass window

and reservoir tank of commercial design It is introduced to either end of the bore tube via two normally closed solenoid valves Needle valves on the outlets of the solenoid valves can be adjusted to vary the exhaust rate of air from the bore tube, and hence the speed of drawer travel A third normally open solenoid valve in the upper line acts as a safety device such that in the event of a break in the electrical circuit or a power failure pressure is immediately applied to the top of the drawer returning it to the safe position

Mechanical support for the drawer in the source exposed position is provided by a solenoid actuated pin which engages in a groove around the drawer body at the same time closing the lower solenoid valve This enables long irradiations to be carried out without maintaining air pressure in the drawer A cable attached to one end of this pin extends outside the shielded room enabling manual retraction in the event of solenoid failure

The facility is operated from a control console outside the shielded room which houses a timer power supply control and source position indicator lights (Fig 3)

The timer has a range of 120 hours in increments of 6 minutes the minimum setting being 18 minutes Shorter exposures can be achieved by manual shut off of the timer

*Installation and room shielding* For economical reasons it was considered necessary to install the unit in a room requiring minimum additional shielding and security measures Such a room was selected in the basement of the Faculty of Medicine (Figs 4 and 5) situated in a corner of the central wing of the building the occupancy of adjacent areas being almost nil

The concrete floor rests directly on bedrock and the two preexisting outside walls already offer considerable radiation protection Above the ceiling an

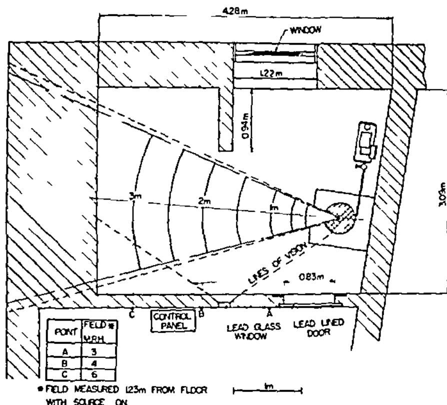



Fig 4 Room projection in a horizontal plane showing the limits of the radiation beam (These fields are reduced to background level when source is in the off position )

empty space (beneath the rear end of the great auditorium) offers protection against radiation scattered upwards Access to the unit is gained via a wide corridor leading to a nearby elevator

Some limitation arose from the fact that the original room had an irregular shape and was not very large approx 19 × 15 × 8 6 (5.8 × 4.5 × 2.6 m) The necessity of additional shielding in the direction of the primary beam reduced the inside dimensions of the irradiation room to approximately 14 × 10 × 8 6 (4.25 × 3.00 × 2.60 m) At the same time, it was thought advisable to have sufficient shielding to allow for possible future increase in the source activity

The unit is mounted on a concrete pedestal such that the axis of the beam is horizontal and at a convenient working height of 1.23 m ( = 48 1/2 ) above the floor To make best use of this shape of room, the central axis of the beam is directed 4 5 toward the outside wall The beam is so collimated that the primary radiation is only absorbed by the one wall which is 80 cm thick standard density (147 lbs per ft³) concrete bricks, added to the existing 50 cm

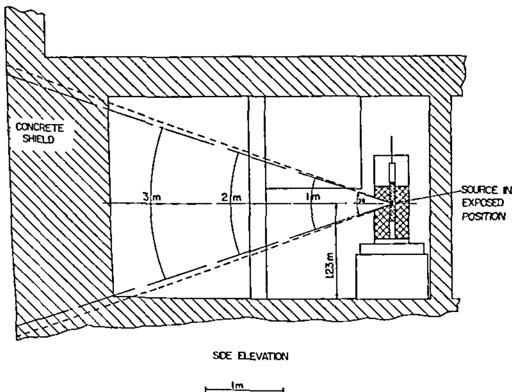



Fig 5 Room projection in a vertical plane

of reinforced concrete in the exterior wall of the building The average half value layer of concrete for $^{60}$Co gamma rays being 5 cm the total thickness of 130 cm corresponds to 26 HVL and offers a dose reduction factor of more than $10^7$ (WACHSMANN 1957) Accordingly, no radiation above background level could be detected outside the building In order to avoid the necessity of filling in the outside window a concrete wall 20 cm thick has been built in the path of scattered radiation The inside protection wall not being exposed to any direct radiation is also 20 cm thick Viewing is carried out through an 8 × 8 (20 × 20 cm) 2 (5 cm) thick high density lead glass window which gives a maximum angle of vision of 110 (shown in Fig 4)

A standard door containing a 5/32 (4 mm) thick layer of lead provides access to the shielded room and is interlocked with the unit in such a manner that the source cannot be raised into the exposed position with the door open Alternatively, opening of the door during an irradiation will immediately return the source to the safe position in less than 2 seconds

Both window and door frames contain layers of lead insuring adequate shielding

The irradiation dose in mr/h at various positions in the control room, when the unit is operating, is given below (position letters refer to Fig 4)

| | A mr/h | B mr/h | C mr/h |
|---|---|---|---|
| At the floor level | 1 | 2 | 3 |
| 1 23 cm above floor level | 3 | 4 | 6 |
| Behind the lead glass window | | 2 5 | |

The field (2 5 mr/h) at the console is not increased when the door is open, therefore the door interlock can be disconnected (in exceptional circumstances) and the unit operated without closing the door (All the above measurements were taken on March 30th 1962 with an A E C I Multipurpose survey meter)

*Animal cages and rack* Rectangular cages, 8 × 8 × 5 (20 × 20 × 12 5 cm), *constructed from 18 g galvanised steel mesh with the entire front hinged* for access contain the animals (rats) during the irradiation

These cages are mounted on a steel framework such that the centre of each cage lies on a point on the surface of a sphere 3 metres in radius By this means, the average dose rate at the center of each cage is constant at 10 6 r hour (on June 20th, 1962) with a uniformity of ± 5 % across the 12 5 cm width

*Dosimetry* In all applications of ionizing radiations one important aspect is that of the accurate measurement of the amount of energy absorbed by the objects undergoing irradiation

In laboratory facilities the object source relationship is generally fixed which permits the dose rate in the sample to be deduced This is done by using a plot of the gamma field in air over the irradiation volume in conjunction with the absorption properties of the material

For subsequent irradiations over a period of time allowance is made for the decay in the activity of the source which can be accurately determined at any time after the original calibration (HOOVER et coll 1955)

An alternative method and one which eliminates any possibility of error, is the use of dosemeters, several types of which are currently available Two examples are ionization chambers and the ferrous/ferric system

*Material and methods* Preliminary measurements were made on the 7th and 8th of February 1962 using a 70 5 medium energy Victoreen condenser chamber of 25 r capacity, covered with a lucite cap to obtain a wall thickness suitable for $^{60}$Co gamma rays Readings were made with a 'model 70 Victoreen condenser r meter

Complete measurements were made between the 16th and the 26th of April *using high energy* Victoreen chambers (models 552 of 2 5 r capacity, and 553 of 25 r capacity) having a nominal wall thickness of 450 mg/cm$^2$ The readings were made with a 'model 570 r meter At this time the source strength was approximately 70 curies

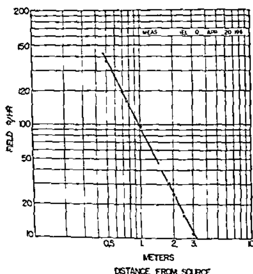



Fig 6 Dose rate (as on 20th of April 196?) in function of the focal distance along the central beam

Both systems had been calibrated less than 1 month before the measurements At all positions, three 5 min exposures were made using the chamber having the most appropriate range generally these readings differed by much less than the ± 5 % rated accuracy The means were calculated and correction made for the 'chamber factor, temperature and atmospheric pressure

## Results

*Doses in the axis of the beam* Fig 6 shows excellent agreement between the two series of measurements for points situated within 2 from the central axis (The figures of the first series are multiplied by 0 975 to correct for the radioactive decay )

It will be seen from the data below that between 70 and 300 cm focal distance there is also good agreement with the inverse square law

| Distance in m | Square of the distance | Dose rate in r/h | r/h × D |
|---|---|---|---|
| 0 5 | 0 25 | 363 | 90 75 |
| 0 7 | 0 49 | 195 | 95 50 |
| 1 | 1 | 99 5 | 99 50 |
| 1 5 | 2 25 | 44 | 99 |
| 2 | 4 | 24 | 96 |
| ?5 | 6 25 | 15 4 | 96 25 |
| 3 | 9 | 10 6 | 95 40 |
| 3 5 | 12 25 | 8 6 | 105 35 |

The dose at 50 cm is too low but an error of 1 cm in the estimated focal distance is sufficient to explain this value The dose at 350 cm is too high this

measurement was made a few centimeters away from the wall and there is obviously significant backscattering at that location

It can be seen that taking an average value of 97 5 for the product of the equation at the end of April, we had by chance in the beginning of February for intermediate focal distances the relation dose × (distance in m)² = 100

In the future this value will decrease directly with the decay of the source activity taken as 100 % on the 5th of February, 1962 The approximate dose-rate (in r/h) at any focal distance and at any time can therefore be readily estimated

It is noteworthy that although this irradiator was especially constructed for chronic low dose rate irradiation of a large target area its simple design makes it suitable for the irradiation of small objects at a very short focal distance i e with a high dose rate e g at a focal distance of 20 cm (at the nozzle of the collimator), the maximum field diameter is 14 cm It can be seen, applying the previous formula that an object the size of a Petri dish can be irradiated at a dose rate of approximately

$$x = \frac{100 \times (100)^2}{(20)^2} = \frac{10^6}{4 \times 10^2} = 2\ 500 \text{ r/h}$$

or 41 7 r/min (in February 1962) Likewise at a distance of 2 cm an object approximately 1 cm³ can be exposed to a dose rate of about 25 × 10⁴ r/h or 4 167 r/min However secondary radiation from the irradiator may be expected to influence the dose rate for samples placed inside the collimator and the irradiation cannot any more be considered as coming from a point source for focal distances shorter than 20 cm The last figures are therefore only a rough guide and will be supplemented by chemical dosimetry done with each experiment

This irradiator is therefore useful for a number of applications ranging from the chronic exposure of large biological objects to radiochemistry

*Field size* The limits (*in the horizontal and vertical planes) are indicated* in Figs 4 and 5 The homogeneous utilizable beam is defined as the region where there is a maximum ± 5 % variation in dose rate between points situated on a spherical surface at equal distances from the source

The penumbra is the region just outside the beam where the dose rate falls *to less than 5 % of its full value (this being the smallest percentage change measurable* by the dosemeters)

The in situ measurements showed a very well defined utilizable beam with a narrow penumbra The homogeneous beam covers an angle of 39 in the horizontal plane and 38 in the vertical plane (Figs 4 and 5) These values are in keeping with the calculated 38 angle of the collimator Taking the penumbra into account, the total beam covers 42° in the horizontal plane 40 5 in the vertical plane The horizontal axis is at a slight angle to the end wall the area of which is covered by the homogeneous beam being a 'distorted circle

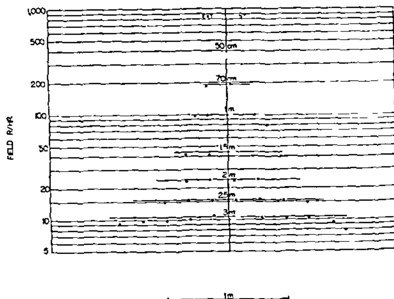



Fig 7 Lateral variation of the dose rates for various focal distances

with a radius varying from 122 to 130 cm and surrounded by a corona of pen umbra 10 cm in width Lines showing the limits of the field and the projections of its axis have been painted on the walls

*Lateral variation of the dose* Fig 7 shows that there is very little lateral dose rate variation in a horizontal plane, situated 123 cm above floor level for focal distances of 70 to 300 cm

Fig 8 shows measurements taken along vertical lines 1 2, 3 and 3 1/2 m away from the source in the central beam The focal distance along these lines increases from the centre towards floor and ceiling and the dose rate diminishes accordingly However, the curvature of the isodose lines is small past 2 m focal distance which means that a parallelepipedic cage arrangement can be used if one is satisfied with a dose variation of $\pm$ 10 to 15 % from one cage to the other

## Practical utilization

This apparatus lends itself to two conditions of irradiation at first thought beyond the limitations of a cobalt irradiator (1) exactly reproducible dose rates at the same focal distances for long periods of time (2) continuously variable dose rates simulating exposure to fallout gamma irradiation

The first is achieved by a composite filter made of a number of thin copper

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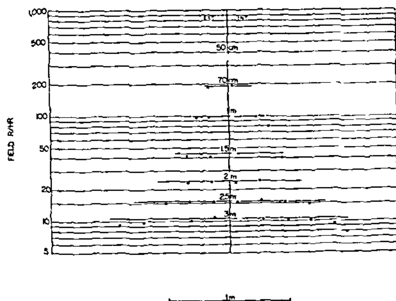



Fig 7 Lateral variation of the dose rates for various focal distances

with a radius varying from 122 to 130 cm and surrounded by a corona of penumbra, 10 cm in width Lines showing the limits of the field and the projections of its axis have been painted on the walls

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The first is achieved by a composite filter, made of a number of thin copper

Fig 8 Variation of the dose rat along ertical
lines in the focal plane

and aluminum layers designed to compensate for the decay of the radioactive emitter

The complete filter placed in front of the collimator will absorb 50 % of the radiation therefore giving an output similar to that without filter one $^{60}$Co half life later (i e 5 3 years)

This half life corresponds to a decay of about 1 % per month Thus by removing every other month a copper layer of appropriate thickness it will be possible to obtain dose rates reproducible within 2 % for more than 5 years, for each focal distance

The second is achieved by a carriage moved at a continuously variable speed along the central beam enabling us to deliver, to animals doses of radiations simulating that of exposure to fallout gamma irradiation The intensity of this irradiation, after a fairly short build up period decreases as a power function of time Our fallout simulator is derived from the comparable assembly built by BAKER at the University of Toronto (BAKER et coll 1961)

Both composite filter and variable speed cage carrier are presently under construction and will be described in a forthcoming paper

Biological work utilizing this equipment has just started and the first experimental results indicate that the LD 50/30 days of Sprague Dawley rats is almost double for a chronic irradiation over a period of 4 days compared with an acute exposure (20 min duration) to $^{60}$Co rays (GHYS et coll 1962)

## SUMMARY

In view of the ever increasing interest in the effects of fallout and chronic irradiation of living organisms it has become necessary to have facilities individually designed to carry out such studies Basic design principles are discussed and the technical description of one such irradiator designed and built at moderate cost is outlined Detailed isodose curves measured with the unit in situ are presented A method for using the irradiator to simulate fallout irradiation conditions is given and the results of the first biological experiments are quoted

## ZUSAMMENFASSUNG

Um dem ansteigenden Interesse uber die Wirkungen von Atomausfall und chronischer Bestrahlung auf den lebenden Organismus gerecht zu werden ist es notig uber spezielle individuell geprägte Einrichtungen zu verfugen die solche Studien zulassen Die Grundprinzipien hierzu werden diskutiert und die technische Beschreibung eines solchen Strahlers der zu moderatem Preis gebaut werden kann umrissen Detaillierte Dosiskurven die mit dem Apparat in situ gemessen wurden werden gezeigt Eine Anwendungsart des Strahlers unter Bedingungen die bei Atomausfallsstrahlung herrschen wird gegeben und die Resultate der ersten biologischen Experimente sind zusammengefasst

## RÉSUMÉ

L étude des effets des retombées radioactives et de l irradiation chronique d organismes vivants suscite de plus en plus d interet Nous discutons les principes de réalisation d irradiateurs spécialement adaptés a ces études et décrivons un tel appareil construit à prix tres modique Nous donnons le relevé détaillé de la dosimétrie faite avec l appareil « in situ » Nous indiquons comment cet irradiateur pourra être utilisé pour simuler l exposition a la composante de retombées radioactives et mentionnons les résultats des premieres expériences biologiques faites au moyen de cet appareil


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# L'EMPLOI DE LA GÉOMÉTRIE DESCRIPTIVE POUR LOCALISER LES SOURCES DE RADIUM, DE RADON ET DE RADIO-ISOTOPES ARTIFICIELS À DES FINS DE DOSIMÉTRIE

par

JEAN-MARC LÉGARÉ

Il y a plusieurs années, PATERSON et PARKER (*in* MEREDITH 1947) et QUIMBY (1953) introduisirent deux plans de répartitions géométriques de sources de radium et de radon. Depuis l'avènement des radio-isotopes artificiels, plusieurs auteurs ont étudié la dosimétrie pour diverses répartitions géométriques de ces sources concrètes (BERCK 1958, 1962; BERCK et coll. 1958; DUTREIX 1961; FRITZ et coll. 1960; FROST 1960; MESHAM et coll. 1954; PIERQUIN et coll. 1959; SHALEK et coll. 1957; WAMBERSIE et coll. 1958).

Tous ces plans, cependant, peuvent se ramener soit à l'idée de dosimétrie uniforme préconisée par PATERSON et PARKER, soit à celle de sources uniformément distribuées de QUIMBY. Les tables de PATERSON-PARKER et de QUIMBY, peuvent parfois être utilisées pour d'autres radio-isotopes si l'on emploie les correctifs de HALE (1958).

Dans tous les cas de radiothérapie interstitielle et d'applications intracavitaires, il est toujours désirable de vérifier si la dosimétrie de la distribution

Soumis à la Rédaction le 13 septembre 1962.

spatiale obtenue correspond bien a celle projetee Des renseignements a ce sujet peuvent etre obtenus de deux manieres générales, notamment au moyen de mesures et au moyen de calculs

1 *Les mesures* peuvent etre directes (A) ou indirectes (B)

*A Les mesures directes* se font au moyen d un detecteur approprie, place a la surface exterieure ou intérieure du corps pres de l ensemble des sources Les renseignements obtenus de cette façon sont tres limites cependant

*B Les mesures indirectes* peuvent etre effectuées à la suite de la reconstruction des sources reelles Cette reconstruction peut etre obtenue a partir de deux radiographies prises sur un ou deux films Il va sans dire que la reconstruction de sources reelles constitue un certain danger

2 *Les calculs* Il a ete demontre avec les annees que parmi les methodes dosimetriques les methodes graphiques sont les plus precises et les plus utiles Une fois que la repartition geometrique est connue les calculs sont effectues a partir des tables appropriees Les methodes actuelles d obtenir cette distribution spatiale sont les suivantes

*A Localisation a partir d une seule pellicule radiographique* La methode du foyer déplace (LEDERMAN et coll 1948) ne requiert qu un seul radiofilm Elle a ete modifiee par TESTA (1957) afin de permettre les calculs de l intensité en chacun des points d interet sans que la reconstruction preconisee par ces premiers ne soit requise

Plus récemment une nouvelle technique n exigeant aussi qu un seul film a ete presentee Cette methode tomographique cependant ne s applique qu a des cas idéaux et quasi ideaux tels que dans les cas d aiguilles paralleles (EGAN et coll 1960 PIERQUIN et coll 1960 1962 SHALEK et coll 1957 STOVALL et coll 1962) De plus une section unique ne donne des renseignements qu a cet endroit et non pas pour l ensemble de la region traitee pour cette raison ces chercheurs ont, en general pris plusieurs sections

*B Localisation a partir de deux films* Un bon nombre d auteurs ont decouvert des moyens de trouver la repartition de sources concretes en se servant de deux radiographies orthogonales (FARR 1953 MEREDITH 1947 SMITH 1958) c est a dire a angle droit Quelques uns ont reconstruit l ensemble des sources au moyen de sources postiches mais la plupart ont determine la repartition sans avoir recours a la reconstruction La methode de calcul est parfois simplifiee par des nomogrammes (HOLT 1956) calculateurs et dispositifs de toutes sortes

En genéral ces methodes de localisation spatiale necessitent suffisamment de calculs de plus elles n evoquent pas toujours les vues que nous desirons obtenir Afin de remedier à ces difficultes une nouvelle méthode est proposee ci bas Elle a comme base la geometrie descriptive Quoique cette methode nous permette d obtenir toutes les vues spatiales quelles qu elles soient les vues les plus utiles aux fins de dosimetrie sont celles de profil et de bout

*Définition et historique de la géométrie descriptive* La géométrie descriptive (LANDREAL 1919) est la partie des mathématiques appliquées qui a pour but de représenter exactement sur un plan, les figures de l'espace et de résoudre à l'aide de la géométrie plane les problèmes où l'on considère les trois dimensions

On peut faire remonter les méthodes et les applications de la géométrie descriptive à la plus haute antiquité mais on peut dire que c'est à MONGE que revient la gloire d'avoir débrouillé le chaos des procédés graphiques employés avant lui dans les arts industriels et d'avoir systématisé les procédés en un petit nombre de principes dans la géométrie descriptive qu'il enseigna à Paris en 1794 et 1795

## Technique de la méthode proposée

Un support de bois (Fig 1) tenant deux cassettes à angle droit a été construit A l'endroit où les deux cassettes se rencontrent une tige métallique a été placée en permanence Cette tige a pour but d'indiquer par la suite (au moyen de sa projection sur chaque film) l'orientation d'un film par rapport à l'autre

2 Un radiofilm est placé dans chacune des deux cassettes Au moment des deux radiographies orthogonales les cassettes seront alternativement insérées à l'intérieur du support de bois

3 Le patient est placé de sorte que les sources concrètes puissent être radiographiées sur les deux films perpendiculaires sans que le patient ne se déplace entre les deux expositions Les sources devront être aussi près que possible des deux films

4 Un anneau de laiton (ou d'un autre métal dense) est placé sur le patient à une distance anneau film égale à la distance sources film vertical La radiographie latérale est ensuite prise à une distance foyer peau suffisamment grande, (1 m environ) afin de rendre la distorsion et le grossissement au minimum Sans que le patient ne se déplace l'emplacement de l'anneau est ensuite vérifié et déplacé si nécessaire de sorte que cette fois-ci il soit à une distance anneau film égale à la distance sources film horizontal Une radiographie verticale est ensuite prise à une distance d'environ 1 mètre

5 Les deux pellicules sont développées et les grossissements de l'ensemble des sources sont déterminés pour chacune des deux images à partir du rapport

$$\frac{\text{Dimension maximale de l'image de l'anneau}}{\text{Diamètre réel de ce même anneau}}$$

Leurs calques sont obtenues sur deux feuilles de papier de soie différentes

6 Ensuite, à partir de ces deux facteurs de correction et d'un pantographe adéquat les deux images sont réduites à leur vraie grandeur sur ces deux feuilles de papier de soie différentes

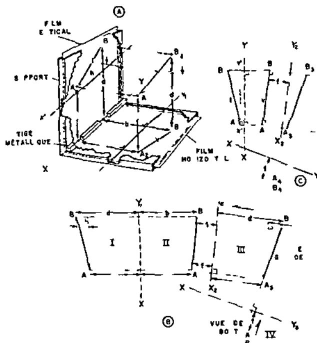


Fig 1 La vraie longueur A B et la vue de bout $A_4B$ d une source linéaire unique s obtiennent à partir des rad ographies à l angle droit corrigees de leur grossissement

7 Ces deux images corrigées telles qu obtenues sur les deux feuilles de papier de soie sont placées au dessus d une visionneuse L une de ces images est deplacee par rapport a l'autre de sorte que les projections de la tige sur chaque film, coincident ou soient paralleles et que des lignes tirees entre les sources ponctuelles (ou les extremités de chacune des aiguilles ou des tubes) correspondantes des deux films soient perpendiculaires aux images des bords superposes de la tige metallique Comme exemple dans la Fig 1 B la vue I est placée relativement a la vue II, de sorte que les lignes $A_1A$ ainsi que $B_1B$ soient perpendiculaires a $X_1Y_1$ (la superposition de l image de la tige sur chacun des films apres avoir ete corrigee du grossissement)

8 Les vues de profil et de bout (ou de face) sont obtenues

9 A partir des tables appropriees l intensite des rayonnements est determinée pour l endroit desire

**Exemples**

1 *Source linéaire unique (Fig 1)*

Celle-ci est considérée en vue d expl quer en détail les fondements de cette méthode graphique Une fois que les sept premières etapes de la section II ont été suivies il s agit ensuite d obtenir les vues de profil et de bout Fig 1 (A) montre l aiguille AB quelque part dans l espace

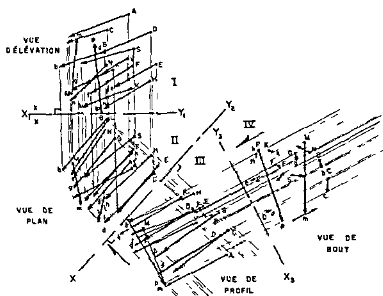



Fig 2 La longeur III et la base IV efficaces de l implantat on cylindrique pro iennent de l application des princ pes de la première figure

A partir de chacune des extremités des aiguilles de la vue II l on trace des lignes de rappel perpendiculaires a la ligne de terre $X_2Y_2$ tout en la traversant

Le long de ces nouvelles lignes de rappel l on rapporte à partir de la ligne de terre $X_2Y_2$ et au delà de celle ci les distances entre chaque extrémité d une aiguille donnée de la vue I et la ligne de terre $X_1Y_1$ tel qu il a été fait dans le cas de l aiguille unique (Fig 1) Tout en em ployant les mêmes lignes de terre et les lignes de rappel appropriées ce procedé est repete pour chacune des autres aiguilles On obtient ainsi les paires de points a A b B c C etc (vue III)

Cette derniere vue ainsi obtenue en tirant les lignes aA bB cC etc est une vue de profil de l implantation d aiguilles puisque la moyenne des aiguilles est vue en vraie grandeur

*Vue de bout* Une ligne de terre $X_3Y_3$ est tracée perpend culairement et a une distance quel conque de l ensemble des aiguilles de la vue III qui forment les cotés lateraux de l implantation cylindrique Tout comme auparavant cette orientation effective est déterminée au moyen de la feuille de papier quadrillé placée sur la visionneuse

Perpendiculairement à $X_3Y_3$ et traversant cette nouvelle ligne de terre l on trace des lignes de rappel émanant de chacune des extrémites des aiguilles de la vue III

A partir de cette ligne de terre $X_3Y_3$ et au-delà de celle-ci l on rapporte pour chacune des aiguilles les distances entre chaque extrémité d une aiguille de la vue II et la ligne de terre $X_2Y_2$ Ces distances sont mesurées le long de ces nouvelles lignes de rappel Ceci nous donne les points a A b B c C etc de la vue IV ainsi construite

Tirons les lignes aA bB cC etc afin de mieux voir les aiguilles dans cette vue IV qui est la vue de bout

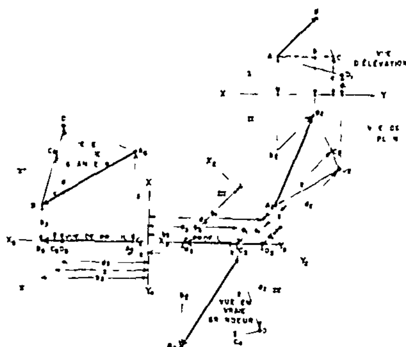


Fig 3 Diverses vues de profil (III V) et de face (IV VI) sont données pou le plan formé par une a guille et un point d intérêt donnés.

*Volume et dosimétrie du cylindre* Le volume aire de la base longueur effective d cylindre La dosimétrie peut être determiné à partir de ce volume et des tables du système de distribution suivi

### 3 *Source linéaire unique et point d'intérêt donné (Fig 3)*

Ce cas est considéré en vue d indiquer les étapes à suivre dans les deux exemples cités plus bas

La droite $A_1B_1$ représente la vue d élévation d une aiguille après que le film vertical a été corrigé du grossissement au moyen du pantographe

La droite $A_2B_2$ est la vue de plan de l aiguille après réduction telle qu indiquée par le grossissement de l anneau sur le film horizontal

La ligne de terre $X_1Y_1$ est obtenue en superposant $x_1y_1$ et $x_2y_2$ qui sont des droites prises parallèles aux projections de la tige sur les films (voir la figure 1)

$D_1$ et $D_2$ sont les projections orthogonales du point d intérêt D situé dans l espace

Après avoir suivi 7 étapes de la technique traçons les lignes $A_1D_1$ $B_1D_1$ $A_2D_2$ et $B_2D_2$

*Vue de profil* A partir de $A_1$ traçons une droite parallèle à la ligne de terre $X_1Y_1$ elle croisera donc $B_1D_1$ en $C_1$ De cette façon la ligne $A_1C_1$ est dans un plan horizontal

De $C_1$ abaissons une ligne de rappel perpendiculairement à $X_1Y_1$ croisant $B_2D_2$ en $C_2$

Tirons la ligne $A_2C_2$ tout en la prolongeant

Perpendiculairement à cette ligne prolongée traçons une ligne de terre $X_2Y_2$ à une distance quelconque de $A_2B_2C_2D_2$

A partir de B et de $D_2$ traçons des lignes de rappel perpendiculaires a $X_3Y_3$
Le long de ces lignes de rappel rapportons les distances $a_1$ $b_1$ $c_1$ et $d_1$ Ceci nous donne les points $A_3$ $B_3$ $C_3$ et $D_3$ (vue III)
Puisque la ligne $A_1C_1$ avait été construite parallèlement au plan horizontal c est à-dire que les côtés $a_1$ et $c_1$ sont égaux il en suit que $A_3$ et $C_3$ coincideront en un seul point
Puisque AC (qui se trouve dans le plan ABD) est vue comme un point $A_3C_3$ dans la vue III il en suit que cette projection III est une vue de profil

*Vue en vraie grandeur* Traçons une ligne de terre $X_4Y_4$ à une distance quelconque de $B_3A_3D_3$ et parallele a cette vue de profil Dans la figure 3 $X_4Y_4$ à été prise à une distance nulle de $B\ A_3C_3D_3$
A partir des points $A_3$ $B_3$ $C_3$ et $D_3$ traçons des lignes de rappel perpendiculaires a $B_3A_3C_3D_3$ ou $X_4Y_4$
Rapportons les distances $a_2$ $b_2$ $c_2$ et $d_2$ le long des lignes de rappel correspondantes Ceci détermine les points $A_4$ $B_4$ $C_4$ et $D_4$
Tirons les droites $A_4B_4$ $A_4D_4$ et $B_4C_4D_4$
Cette nouvelle vue IV obtenue en regardant le plan $B_3A_3C_3D_3$ perpendiculairement est la vue en vraie grandeur du triangle ABD

*Dosimétrie* Puisque $A_4B_4D_4$ représente le triangle ABD vu en vraie grandeur la vraie distance perpendiculaire entre D et AB peut être mesurée sur la vue IV De plus nous pouvons mesurer a quelle distance du centre de l aiguille AB cette ligne perpendiculaire se trouve
De ces données et des connaissances de la source radio-active la dose au point D peut être determinée en employant les tables appropriées
La dosimetrie au point D peut etre obtenue directement de la vue IV si nous possédons l isodose de l aiguille

*Remarques* Dans la Fig 3 deux vues auxiliaires (vue de profil et vue en vraie grandeur) ont été ajoutees Ces projections permettent de mieux voir comment fonctionne la geométrie descriptive Elles aideront aussi a mieux saisir les vues de la figure 4
Prolongeons la droite $B_3A_3C_3D_3$ et traçon une ligne de terre $X_4Y_4$ perpendiculaire a cette première droite
Rapportons au-dela de $X_4Y_4$ les distances prises entre la ligne de terre $X_2Y_2$ et les points $A_2$ $B_2$ $C_2$ et $D_2$ qui la précedent
Puisque ABCD apparait dans la vue III comme une ligne $B_3A_3C_3D_3$, il en suivra que la vue de bout de cette projection donnera *une autre vue de profil* $B_5C_5D\ A_5$
Prenons une ligne de terre $X_5Y_5$ parallele à la droite $B_5C\ D\ A_5$
Traçons les lignes de rappel perpendiculaires a $X_5Y_5$ Ces droites sont tracées à partir des points $B_5$ $C_5$ $D_5$ et $A_5$
Rapportons les distances $b_2$ $c_2$ $d_2$ et $a_2$
Tirons les lignes $A_6B_6$ $A_6D_6$ et $B_6C_6D_6$
Cette nouvelle vue VI est *la vue en vraie grandeur* du triangle ABD et elle est identique à la vue IV Comparer les deux vues
Il est a noter que la vue IV n a pas été employée ici puisqu elle ne se trouve pas sur le chemin entre les vues V VI et les deux premières vues

4 *Implantation plane de grains radio actifs (Fig 4)*

Les vues I et II représentent le film vertical (la vue d élévation) et le film horizontal (la vue de plan) après que les sept premieres étapes de la technique ont été suivies Les grains sont représentées par les lettres a b c d e f g h i j k et l

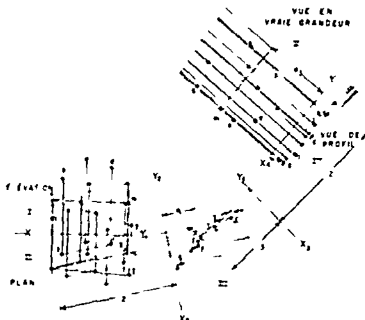



Fig. 4. La vue de face X d'une implantation plane de grains radioactifs est obtenue en trouvant d'abord une vue de profil IV effective

*Vue de profil.* Dans la vue d'élévation, prenons trois points (grains), deux vers l'extrême droite ou gauche et un autre à l'autre extrémité.

Tirons les lignes entre ces 3 points qui sont pris suffisamment espacés.

A partir du point a, traçons une droite parallèle à la ligne de terre $X_1Y_1$ et rencontrant la ligne cg en m (vue I).

De m (vue I), abaissons une ligne de rappel perpendiculaire à $X_1Y_1$ et rencontrant cg en m (vue II).

Dans cette vue II, tirons la nouvelle ligne am et prolongeons la. Cette nouvelle ligne am (vue II) est en vraie grandeur, puisque dans la vue I la ligne am avait été prise parallèle à $X_1Y_1$, c'est-à-dire que la projection orthogonale am (de la ligne AM appartenant au triangle ACM) de l'implantation plane située quelque part dans l'espace) sur la vue d'élévation est parallèle à la ligne de terre $X_1Y_1$.

Le long du prolongement de la ligne am (vue II), traçons une nouvelle ligne de terre $X_2Y_2$, perpendiculaire à am de la vue II.

Au-delà de $X_2Y_2$ et le long du prolongement de am de la vue II, rapportons les distances entre les points a, m (vue I) et $X_1Y_1$. Les nouveaux points a et m (vue III) coïncident donc en un seul et unique point, puisque les distances rapportées ($a_1$) sont identiques.

A partir de chacun des points de la vue II, traçons des lignes de rappel perpendiculaires à $X_2Y_2$ et rapportons y les distances entre les points de la vue I et la ligne de terre $X_1Y_1$.

Cette vue III est une vue de profil de l'implantation plane des grains A, B, C, D, E, F, G, H, I, J, K, L, pourvu que l'implantation se trouve sur un plan idéal. Ceci est vrai puisque les points A et M sont vus en un seul et unique point.

*En général, les grains ne sont pas sur un plan idéal. Dans ce cas, les grains ne paraissent pas* sur une ligne droite dans la vue III. En telle situation, la vue III est plutôt une approximation

de la vue de profil la déviation étant d autant plus grande que le triangle formé par les trois grains arbitrairement choisis n est pas parallèle au plan efficace des grains Pour réduire cette erreur au minimum regardons de bout le plan (vue III) de grains qui est quelque peu tourné sur lui même autour de la forme allongee que forme l ensemble des grains de la vue III Cette nouvelle vue nous donnera une vraie vue de profil

Traçons une ligne de terre $X_3Y_3$ perpendiculaire a la forme allongée des grains de la vue III et à une distance quelconque de ceux ci

A partir de chacun des points (vue III) traçons des lignes de rappel perpendiculaires a $X_3Y_3$ et traversant celle ci

Rapportons a partir de $X_3Y_3$ les distances entre les points de la vue II et la ligne de terre $X_2Y_2$ comme il a été fait pour le grain A

Cette nouvelle vue IV est une vue de profil

*Vue en vraie grandeur* Traçons une ligne de terre $X_4Y_4$ perpendiculaire a la forme longitudinale de l ensemble des grains de la vue IV cette ligne est prise à une distance quelconque de l ensemble des grains de la vue IV

A partir de chacun des grains (vue IV) traçons des lignes de rappel perpendiculaires à la ligne de terre $X_4Y_4$ et allant au dela de celle ci

Pour chacun de ces grains rapportons les distances entre les points de la vue III et $X_3Y_3$ tel qu il a été fait pour le point A (distance $a_3$)

La nouvelle vue V est la vue en vraie grandeur (vue de face) de l implantation plane

*Dosimetrie* Maintenant que l aire de l implantation est connue (vue V) la dose a la région traitée s obtient a partir des tables du système de dosimétrie choisi

5 *Application de radium intracavitaire — cancer du col utérin* (*Fig* 5)

Fig 5 montre les vues d élévation et de plan d un tandem et de deux tubes radio-actifs lesquels proviennent chacun d un groupe de tubes situés dans deux ovoides differents Le tandem pointe vers le bas dans la vue d élévation parce que dans cette application l utérus a été renversé

La vue I represente la vue d élévation Cette vue de l image corrigée du grossissement s obtient en prenant une radiographie orthogonale sur un film vertical en la réduisant au *moyen du pantographe* Nous pouvons aussi obtenir cette vue en se servant de la methode de TESTA Contrairement a cette première méthode la double exposition sur un même film nous donne la vue de plan en plus

La vue de plan représente la projection non grossie du tandem et des deux tubes sur un plan horizontal $X_1Y_1$ représente la ligne de terre entre ces deux vues

*Localisation des deux points 1 par rapport au tandem* Les deux points A (ind qu es comme A et A afin de les distinguer) seront localisés d après la plus récente definition S HEER 1962) de ce point Tout d abord nous devons obtenir le plan vertical passant par l t dem vu en vraie grandeur

Traçons une ligne de terre $X_2Y_2$ parallèle à l image du tandem dan l v ue (II) de plan et à une distance quelconque

A partir des deux extrémités du tandem et des deux tubes (vue II traçons des lignes de rappel perpendiculaires a $X_2Y_2$ et allant au dela de cette ligne de terre

Le long de ces lignes de rappel rapportons les distances correspondantes entre les extrémités du tandem de la vue I et $X_1Y_1$ c est à-dire les distances $a_1$ et $b_1$ Tirons cette ligne

Ceci donne un plan vertical contenant le tandem en vraie grandeur (vue III) Comparer à la figure 1

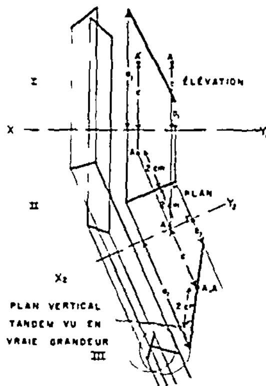



Fig. 5. Les deux points A peuvent être localisés dans les plans vertical I et horizontal II lorsque nous avons déterminé le plan vertical passant par le tandem vu en vraie grandeur III et la projection des tubes des deux ovoïdes sur ce plan.

Rapportons aussi au-delà de $X_2Y_2$ les distances entre chaque extrémité des tubes de la vue I et $X_1Y_1$. Tirons les lignes dans cette vue III.

Ceci donne les projections des tubes sur le plan vertical (vue III).

Autour de ces tubes de la vue III, traçons les surfaces extérieures des ovoïdes.

Partant de la moyenne de ces surfaces extérieures, traçons une ligne perpendiculaire au tandem vu en vraie grandeur et rencontrant celui-ci (vue III).

A partir de cette intersection, mesurons (deux) 2 cm le long du tandem vu en vraie grandeur tout en s'éloignant des deux ovoïdes. Ceci détermine les deux points A.

*Dosimétrie du tandem.* La dosimétrie aux points A (A et A) peut maintenant être déterminée pour ce tandem puisque de la vue III (plan vertical vu en vraie grandeur) nous pouvons mesurer à quelles distances ces deux points A se trouvent des bouts du tandem. Aussi nous savons que les points A se trouvent à une distance perpendiculaire de 2 cm de celui-ci.

*Points A et A dans la vue de plan.* Partant de AA de la vue III, traçons une ligne de rappel perpendiculaire à $X_2Y_2$ et traversant celle-ci et le tandem de la vue II.

Le long de cette ligne de rappel déterminons les points A et A en les plaçant a 2 cm de chaque coté du tandem (vue II) Ceci est justifie par la définition des points A la droite tirée entre ces deux points A et croisant le tandem perpendiculairement se trouve parallèle au film horizontal

*Points A et A de la vue d élévation* Partant des points A et A de la vue (II) de plan traçons des lignes de rappel perpendiculaires a $X_1Y_1$ et allant au-delà de celle-ci

Le long de ces lignes de rappel rapportons a partir de $X_1Y_1$, la distance entre A et $X_2Y_2$ et celle entre A et $X_2Y_2$ c est a-dire les distances $c_1$ Ceci détermine nos deux points A ( A et A ) dans la vue d élévation

*Dosimetrie des tubes des ovoides* Les deux points d intérêt A et A sont donc situés par rapport aux deux ovoides pour les vues d élévation et de plan

Construisons 4 paires de triangles au moyen des deux tubes et des deux points A des vues d elévation et de plan Pour chacune des 4 paires de triangles repétons le procedé de la figure 3 tout en employant la même ligne de terre $X_1Y_1$

*Remarques* Il existe une méthode plus simple de localisation Elle est généralement justifiable due aux grandes distances entre un tube choisi et chacun des points A Dans cette methode nous prenons les sources linéaires comme étant ponctuelles De cette façon l on est ramené a obtenir 4 lignes en vraie grandeur (la droite entre le point central d un tube et un point A)

Pour obtenir ces quatre lignes il s agit de répéter la procédure de la figure 1 quatre fois Les lignes de terre (sauf $X_1Y_1$) seront cependant différentes pour chacun de ces quatre cas

Une fois que ces 4 distances sont obtenues en vraie grandeur les intensités peuvent être obtenues a partir des tables en tenant compte du nombre total des tubes dans chacun des ovoides

Une fois que l on connait suffisamment les méthodes de géométrie descriptive nous pouvons soustraire quelques étapes

A l une des extrémités de $A_2B_2$ (Fig 1) rapportons perpendiculairement a $A_2B_2$ la difference des hauteurs (cotes) des points $B_1$ et $A_1$ viz la distance d—c L hypothénuse mesurée est la distance en vraie grandeur entre les points A et B situés quelque part dans l espace

## Discussion

Nous remarquons de la figure 1 que le support de bois n est pas requis pourvu que le bord du film vertical soit parallele au dessus de la table et que le cote latéral du film horizontal soit parallele au cote lateral de la table

VREELAND a deja donné une methode de correction pour la distortion d images sur les radiofilms Celle ci est negligeable si les conditions suivantes sont mises en pratique

1 Grande distance foyer sources
2 Courte distance film sources
3 Épaisseur et largeur de l ensemble des sources petites par rapport a la distance foyer film
4 Anneau et sources a distance egale du film
5 Films bien places et faisceaux suffisamment perpendiculaires aux films
6 Patient non deplacé entre les deux expositions

Lorsque les grossissements pour les deux films sont identiques, il n'est pas nécessaire de réduire chacune des deux images. Il s'agit tout simplement d'en tenir compte dans les dimensions finales avant de référer aux tables et isodoses.

Les tables de radium citées (GLASSER et coll., GREENFIELD et coll., MEREDITH, VERHAEGEN) sont presque toutes calculés à partir des données de SIEVERT (1932). Les tables du système de Manchester (MEREDITH 1947) ont été refaites par JOHNS (1961); elles ont été multipliées par le facteur

$$\frac{1}{0.965} \cdot \frac{8.4}{8.25} = 1.055$$

Ces nouvelles tables tiennent maintenant compte de la plus récente valeur de l'activité spécifique d'une source ponctuelle de radium (ATTIX & RITZ 1957). Elles sont alors exprimées en

$$\frac{\text{mg h}}{1\,000 \text{ rad}}$$

On remarque dans la méthode de géométrie descriptive décrite que toutes les distances rapportées le long des lignes de rappel proviennent de la deuxième vue précédante ou la deuxième suivante si l'on revient en arrière. Les distances rapportées pour obtenir la vue III proviennent de la vue I, celles de la vue IV proviennent de la vue II, etc.

Dans tous les exemples cités, la convention habituelle de lettrer n'a pas été suivie. Les indices ont été choisis d'une telle façon qu'en rapportant les distances, les indices des points et de chaque ligne de terre soient les mêmes. Comme exemple, $a_1$ est la distance entre le point $A_1$ et la ligne de terre $X_1Y_1$, $a_2$ est la distance entre $A_2$ et $X_2Y_2$. Les lignes de terre étant conventionnellement pointillées sont ici généralement représentées par des lignes très minces.

Toutes les implantations d'aiguilles parallèles ainsi que celles de grains formant des cubes du type BERGS (BERGS 1958 et BERGS et coll. 1958) se résolvent en suivant l'exemple du cylindre (Fig. 2).

La précision de la méthode a été déterminée pour des implantations non idéales d'aiguilles postiches et de grains non radio-actifs. Les variations maximales des dimensions finales étaient de 5 %.

## RÉSUMÉ

Une méthode graphique de localisation des sources radio-actives est décrite. Elle est ensuite illustrée pour une implantation cylindrique de sources linéaires, une implantation plane de grains radio-actifs ainsi que pour une application intracavitaire de radium.

## SUMMARY

A graphical method of localizing radioactive sources is illustrated by means of a cylindrical implantation of linear sources, a single plane implantation of radioactive grains and an intracavitary application of radium.

## ZUSAMMENFASSUNG

Eine graphische Methode fur die Lokalisierung von radioaktiven Quellen wird bildlich erlautert und demnach werden eine cylindrische Implantation von linearen Strahlenquellen eine offene Einzel Implantation radioaktiver Korner wie auch eine Übertragung in intra cavitaren Radiumquellen illustriert

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# BOOK REVIEWS

BIOLOGISCH CHEMISCHER STRAHLENSCHUTZ EINE ÜBERSICHT in TABELLEN Von R Huber und E Spode Akademie Verlag Berlin 1962 Price 124 DM

The menace of nuclear war and the enhanced risk of radiation accidents by the increasing use of nuclear energy have drawn attention to the possibilities of chemical and biologic protection against radiation injury The research activity in this field has been extensive and an enormous number of papers have been published although the absence of a bibliography covering the whole field seems conspicuous

Reports reviewing the literature dealing with attempts to alter the response of animals to ionizing radiation were published as early as 1949 and in 1951 and 1953 by SELLE et coll from the University of California Los Angeles HUBER and SPODE have now with German thoroughness prepared a survey in tabular form of the works on biologic and chemical radioprotection covering a time period from 1945 to 1959/1960 The large amount of work within this field is illustrated by the number of references close on 1 600 By far the greatest number of investigations have been carried out on the effects of SH compounds and related substances Bone marrow transplantations play a dominant role among the many attempts to obtain therapy against acute radiation injury Other substances surveyed include hormones amino acids amines heterocyclic compounds and proteins alcohols carbohydrates and organic acids and vitamins and related compounds Attention is also paid to the influences on the vegetative as well as the central and peripheral nervous system parabiosis and transfusion antibiotics and sulphonamides cyan compounds and other enzyme toxins and antihistamines The survey appears to be almost complete and will be of great value as a reference to those working in the field of chemical and radiobiologic protectors

The use of a special device with sharp-edged rings that cut the leaves detracts from the loose leaf system which in itself seems an excellent idea It is to be hoped that a different kind of cover will be used in the next edition The price of DM 124 appears to be rather high

*Arne Nelson*

THE TOXICOLOGY OF RADIOACTIVE SUBSTANCES Vol 1 STRONTIUM CAESIUM RUTHENIUM RADON Editors Letavet and E B Kurlyandskaya Translation from the Russian edited by E Lloyd 236 pages 113 figures and 67 tables Pergamon Press Oxford 1962 Price 80 Sh

Access to the comprehensive Russian scientific literature has to a great extent been hampered by the language barrier The increasing number of translations into English has now made this volume available to Western readers who are presented with an account of Russian progress in the study of the effects of isotopes of strontium caesium ruthenium and radon in experimental animals

The Russian original was published in 1957 and the work reported was carried out from 1951 to 1953 The interpretation of some of the results have been modified by the editors of the English edition in the light of later investigations Most of the experimental results are however still valid and of great interest in spite of the long time lapse between the appearance of the Russian and English versions

There are four main sections (1) Absorption distribution and excretion (2) Radiotoxic effects in high dose experiments (3) Radiotoxic effect of radioactive ruthenium caesium and strontium in continuous experiments (4) Stimulation of the excretion of radioactive strontium and caesium from the organism

KURLYANDSKAYA emphasizes the importance of studying the reactions of the organism during the continuous internal administration of small doses of radioactive substances The papers included are therefore mainly concerned with the biologic effects of radioisotopes under continuous intake (2 to 3 years BURYKINA reports a much higher resorption of ruthenium 106 from the gastrointestinal tract 100 to 200 times higher than that given by certain early American investigators This difference is probably due to the particular chemical forms used which especially in the case of ruthenium will complicate the metabolism KURBASOVSKAYA and USHAKOVA have studied the transfer of Sr 89 and Sr 90 from mother to foetus in rats and have established that the accumulation of strontium in the foetus is mainly due to the isotope received during pregnancy This has been confirmed by the reviewer and his co-worker in an investigation in mice which also showed that the foetal uptake coincides with the ossification of the foetal skeleton and begins approximately at the 14th day of gestation The strontium deposition in the females prior to gestation is of minor importance It is stated that a subcutaneous dose of Ru 106 gave a more marked distribution of the leukopoiesis and erythropoiesis than Sr 89 Sr 90 and Cs 134 An investigation of the chronic effect of these isotopes administered per os in rabbits revealed however that radiostrontium caused more extensive damage to the erythropoiesis than was evident after Cs 134 and Ru 106

The last part of the book deals with the search for agents that stimulate the excretion of radioactive substances All the classic methods have been tried with only slight effects

The book constitutes an excellent review of the extensive work in the U S S R on the biologic effects of radioactive isotopes The pictorial material is not uniform however The legends give no information on staining methods or magnification and the few autoradiograms are primitive compared with the standards set by the autoradiograms of ULLBERG and co-workers in this country Any statistical treatment is conspicuously absent

*Arne Nelson*

FILMDOSIMETRIE GRUNDLAGEN UND METHODEN DER PHOTOGRAPHISCHEN VERFAHREN ZUR STRAHLENDOSISMESSUNG Von Klaus Becker 176 Seiten 93 Abbildungen Springer Berlin 1962 Price 24 DM

A short introduction on the various kinds of radiation and the fundamental concepts of dosimetry is followed by a more detailed account of photographic processes the properties of different emulsions and developers and densitometry The main part of the book is devoted to the various methods of photographic dosimetry Emphasis is laid on radiation protection measurements while other uses are touched upon more lightly The difficulties and sources of error especially when measuring radiation of unknown quality or mixed radiations (e g gamma rays and neutrons) are discussed in detail and advice given on the precautions that should be observed Theoretical foundations as well as practical information on film badge design and the organisation of a radiation protection service are considered and discussed in detail

The book ends with a long and useful list of references It is however a pity that many papers bear only a code reference consisting of a few letters and figures so that their tracking is difficult without access to a specialized library an indication of the institutes of origin would have been helpful

The reviewer considers the book to be of great value to all those working theoretically or practically in the field covered

*Sven Benner*

# ACTA RADIOLOGICA

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# A MODIFIED COBALT 60 APPLICATOR FOR THE TREATMENT OF RETINOBLASTOMA

by


BENGT H O ROSENGREN and BJORN TENGROTH


Numerous methods for the treatment of retinoblastoma have been proposed during recent decades The present method of choice is some form of radiation therapy with or without the concomitant administration of radiomimetics

Retinoblastoma is a malignant tumour arising from the retinal germ cells it occurs almost exclusively in infancy and childhood and is frequently con genital Among eye tumours the growth is second in frequency to melano sarcoma of the uvea The tumour is present in both eyes and often in some 30 per cent of the cases has a multilocular character

Retinoblastomas are highly malignant and without treatment the prognosis quo ad vitam is extremely grave The tumour may either spread via the optic nerve to the cavity of the skull and orbit or by metastases through the blood paths

Enucleation until the late 1920 s was the only chance of saving the life of an affected child After FOSTER MOORE in 1929 had introduced therapy with ionizing radiation from radium and particularly after diathermy (WEVE 1932) had come into use attempts were made to treat the less affected eye in cases


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of bilateral retinoblastoma while the other eye was enucleated, in unilateral cases the affected eye was enucleated. Diathermic treatment of the tumour itself (WEVE 1932, DUNPHY 1957) or photocoagulation of the vessels entering it (MEYER-SCHWICKERATH 1959) has occasionally resulted in healing. The risk of recurrence or of large intra-ocular haemorrhages must, however, be deemed comparatively great.

Whereas some workers (REESE et coll. 1955, 1957, 1958) have claimed excellent results with a combination of roentgen irradiation to the eye and parenteral radiomimetic (triethylene melamine, TEM) therapy, other workers using this mode of treatment (ERICSON & ROSENGREN 1961) have failed to achieve equally good results. The intravenous or intra-arterial injection of TEM, owing to its necessarily parenteral administration, must constitute a considerable risk of inducing systemic lesions. The TEM concentration in the tumour admittedly may become high and the radiomimetic activity adequate, but lesions, particularly of the bone marrow, make the use of the drug hazardous. The benefits of TEM therapy will be realized only in the care of clinicians who have considerable experience of the drug's administration and thorough knowledge of its narrow range of application. Therapy with intravitreous Thiotepa (Tifosyl) injections has been tried (ERICSON & ROSENGREN 1961) but it merely produced temporary improvement. Since the interchange between tumour tissue and vitreous is not understood, the Tifosyl concentration in the former cannot be estimated and it probably does not attain the intended level.

Roentgen irradiation to the entire eye suffers from obvious disadvantages. The doses commonly given, 3 000 to 4 000 r (REESE recommended a total dosage of 8 000 r in divided doses of 400 r), have almost invariably been accompanied by cataract formation, frequently by necrosis of the vascular walls leading to intra-ocular haemorrhage, and not infrequently by phthisis bulbi. The limit for the risk of phthisis appears to lie around 5 500 r.

Treatment with radioactive applicators was initiated in 1929 by FOSTER MOORE, who used radon needles inserted into the tumour, and was later modified in various ways (WALDMAN 1940, JOYCE 1944, JOHNSTON 1949). STALLARD (1948) introduced his so-called radium disk, a specially designed radium applicator of platinum formed in a thin shell having the same curvature as the sclera and capable of being sutured to the sclera outside the tumour. This applicator was further modified by substituting the isotope $^{60}Co$ for the radium preparation. In 1952, STALLARD surveyed the results of therapy in the series of retinoblastoma cases he had treated over the previous 20 years with both roentgen irradiation and radon needles, as well as with radium and $^{60}Co$ applicators, the results of corresponding treatment in other workers' series being used as a basis for comparison. He came to the conclusion that treatment with radium and cobalt applicators was preferable to roentgen irradiation of the whole eye when the retinoblastoma covered less than one-



Fig 1 Co applicator with ring for attachment

third of the retina Effective immobilization of the child s head was absolutely essential when roentgen irradiation was employed There was a high incidence of late complications in the form of haemorrhages and retinal detachment if the dosage was to be effective

Radium and cobalt applicators are so shaped that they can be located over the retinoblastoma Owing to their close proximity to the tumour, they make it possible to expose it to relatively large radiation doses which decaying geometrically, do not unduly affect surrounding tissues Only $\gamma$ radiation is utilized The results achieved with these applicators indicate that complications are relatively few and rare The lens receives a comparatively small radiation dosage a fact which reduced the incidence of cataract in STALLARD s series

Pending the advent of better procedures based on entirely new principles the fact that an applicator can reach a circumscribed retinoblastoma without unduly harming surrounding tissues must make its use the method of choice for the treatment of solitary retinal neoplasms of up to 10 mm in diameter

Novel therapeutic methods have also been tried One such method the electron irradiation of extensive retinoblastomas with lead shielding of the lens has yielded encouraging results but the number of cases is still too small to justify a final verdict (HULTBERG 1962) BECKER of Heidelberg described another modification A further interesting possibility is the utilization of the so-called *Bragg peak in high energetic proton irradiation*

Progress in the field of retinal surgery has contributed a number of methods and attachments for achieving scleral buckling One such device the so-called scleral buckler has been used routinely for a number of years in our clinic (ROSENGREN 1960) It consists of a ring to which is soldered a curved arm carrying a small ball or cylinder at its free end the whole assembly being made of silver In practice a unit with an arm of suitable length for the application in mind is selected and the arm is manoeuvred backwards along the bulbar wall extraconjunctivally or transconjunctivally until the ball or

cylinder is located at the required point on the exterior of the bulb. The ring is then fastened around the limbus with a few episcleral sutures. When the arm is bent, the attached ball or cylinder buckles the sclera. The resultant retinal incurvation is visible in the ophthalmoscope and allows final adjustments to be made. This type of scleral buckler has proved to be especially suited for the treatment of retinal detachment with solitary ruptures.

The scleral buckler has now been modified by replacing the silver ball or cylinder on the arm with a platinum sphere containing $^{60}$Co, thus converting the device into a versatile cobalt applicator (TENGROTH 1962). By virtue of the scleral incurvation, the precise position of the applicator may be checked and, if necessary, corrected under ophthalmoscopic control by bending the arm. The ball or cylinder is thus pressed against and into the base of the tumour. Consequently the tumour will more or less envelope the applicator and the dose will be adequately distributed. As mentioned, a series of rings with different arm lengths is available, the arms being screwed into a socket in the cobalt sphere (see Figs 1 and 2).

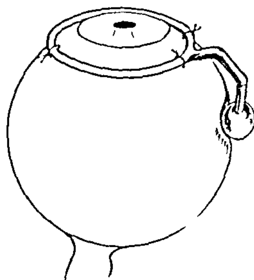


Fig 2 Principle of attachment of [illegible] applicator

Before one of STALLARD's $^{60}$Co disks can be applied it is necessary to locate the projection of the tumour on the sclera, a time-consuming procedure. Furthermore, attachment of the applicator may require that one or more of the extra-ocular muscles be cut, thus prolonging the duration of the operation still more. Lastly, removal of the applicator demands that the posterior bulbar segment be exposed, subjecting the subject to the stress of another almost as lengthy session under anaesthesia. Such exposures of the sclera become even more difficult if the patient has previously received irradiation therapy of some kind because the excision of fibrotic tissue called for in such cases is attended by massive haemorrhages in the operation field.

This $^{60}$Co sphere has proved as simple to apply as the scleral buckler. No manifest necrosis has been induced by compression and irradiation of the interposed conjunctiva. A tumour situated in the posterior segment of the eyeball may conveniently be approached by inserting the arm through a minute conjunctival incision, the operation may be made under light anaesthesia. The applicator is removed by first cutting the episcleral sutures around

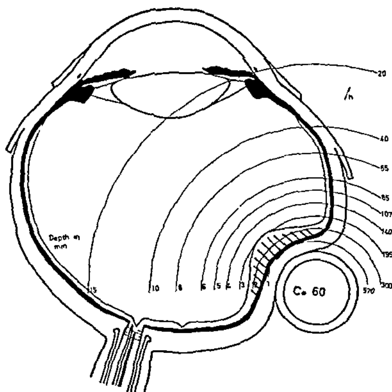



Fig 3 Isodose curves showing dose rate in r per hour

the limbus and then extricating the arm and sphere by a gently twisting movement This procedure may readily be carried out under local anaesthesia and a $^{60}$Co sphere applied extraconjunctivally may be removed without any anaesthesia whatsoever

*Radiation data for the $^{60}$Co sphere* The $^{60}$Co applicator has the shape of a near sphere with an external diameter of 6 mm An internally threaded hollow stud is provided as a means of attachment to the arm (see Fig 1)

The radioactive cobalt component is enclosed in a 0·5 mm thick platinum shell The current designs have an activity of 8 mC (isodoses see Fig 3)

As manufactured the sphere is charged with $^{59}$Co which subsequently has been activated in a neutron reactor at Amersham England

Our source has a higher activity as compared to STALLARD's cobalt desk, another dose rate and therefore another fractionation (dose time relationship) is consequently used The treatment time is about 24 hours giving about 12 000 r at 1 mm depth This dose seems to be comparable with the 19 000 r administered in about 100 hours by STALLARD

**Table 1**

*Doses in r at increasing depth*

| | | 1 | 2 | 3+4 (Booster to 1) |
|---|---|---|---|---|
| Fields | | 1 | 2 | 3+4 (Booster to 1) |
| Date | | 11.11. 1960 | 5.4. 1961 | 25.5. 1961 |
| Depth in mm | 1 | 12 000 r | 6 000 r | 10 000 r |
| | 2 | 6 300 r | 3 200 r | 5 300 r |
| | 3 | 4 100 r | 2 000 r | 3 400 r |
| | 4 | 3 000 r | 1 500 r | 2 500 r |

**Table 2**

*Doses in r at increasing depth*

| | | 1 | 1 a (Booster to 1) |
|---|---|---|---|
| Fields | | 1 | 1 a (Booster to 1) |
| Date | | 20.9. 1960 | 25.10. 1960 |
| Depth in mm | 1 | 10 000 r | 6 000 r |
| | 2 | 5 300 r | 3 200 r |
| | 3 | 3 400 r | 2 000 r |
| | 4 | 2 500 r | 1 500 r |

## Case reports

*Case 1.* Boy, aged 3 years, with bilateral retinoblastoma. The left eye had been enucleated in another hospital and the right eye had received a total dose of 4 900 r combined with intravenous TEM administration. The patient was transferred to our eye department because large tumour masses were still present on the fundus. A cobalt sphere was applied for 10 hours in November 1960; dosage particulars are given in Table 1. Two weeks later the tumour was found to be disintegrating. Owing to the discovery of a further tumour arising from another part of the fundus, a $^{60}$Co sphere was again inserted for 5 hours in April 1961 (see Table 1), and two weeks later this tumour was much smaller. As a booster dose to field 1 in May 1961 failed to prevent a general recurrence the right eye had to be enucleated.

*Case 2.* Girl, aged 12 months, with bilateral retinoblastoma, in whom the fundus had been practically covered with tumour tissue when the left eye was enucleated. A tumour of the right eye, 6 optic disk diameters across, was treated by repeated photocoagulation of the vessels supplying the tumour and once by diathermy. While this treatment was in progress a large intra-ocular haemorrhage occurred. Somewhat later, when the blood had been absorbed, the tumour was seen to have grown. At this stage, in September 1960, a cobalt sphere was applied, the estimated dose being given in Table 2. The cobalt sphere was re-applied a month later, as tumour tissue persisted. After another month the tumour had diminished appreciably, the reduction progressing until the tumour had completely healed. At control examination 26 months later the sole sequela was a retinal scar. The patient's ocular fixation was then adequate, with central vision, but on account of her age the visual acuity could not be measured satisfactorily. (The patient was last seen in September 1963.)

*Case 3.* Boy, aged 12 months, with bilateral retinoblastoma, whose left eye had been enucleated as the fundus had been almost completely covered by growth. Examination of the right eye disclosed the presence of two tumours of 2 and 4 optic disk diameters, respec-

**Table 3**

*Doses in r at increasing depth*

| Fields | | 1 | 2 | 3 |
|---|---|---|---|---|
| Date | | 21 11 1961 | 5 12 1961 | 9 1 1962 |
| Depth in mm | 1 | 12 500 r | 12 500 r | 12 500 r |
| | 2 | 6 600 r | 6 600 r | 6 600 r |
| | 3 | 4 300 r | 4 300 r | 4 300 r |
| | 4 | 3 100 r | 3 100 r | 3 100 r |

**Table 4**

*Doses in r at increasing depth*

| Fields | | 1 | 1 a (Booster to 1) |
|---|---|---|---|
| Date | | 18 1 1962 | 8 5 1962 |
| Depth in mm | 1 | 10 000 r | 7 000 r |
| | 2 | 5 300 r | 3 700 r |
| | 3 | 3 400 r | 2 400 r |
| | 4 | 2 500 r | 1 700 r |

tively which were irradiated from a $^{60}$Co sphere The first focus was treated in November and the second 2 weeks later the doses being similar (see Table 3) A further two weeks later a new third focus measuring 3 optic disk diameters was detected and was treated in a corresponding manner in January 1962 The tumours were appreciably smaller two months later and four months after the last cobalt application exhibited no signs of progression there were no indications of any new foci Twelve months after the last application the retina merely presented signs of healed foci There was no evidence of any new tumours or of recurrence in the old scars (August 1963)

*Case 4* Boy aged 2 years with bilateral retinoblastoma, whose right eye had been enucleated because of diffuse infiltration A cobalt applicator was positioned in the left eye in January 1962 against a tumour 9 optic disk diameters across which received the doses specified in Table 4 Some 4 months later the retinoblastoma was still present but was distinctly smaller Another cobalt applicator was introduced on 6 May 1962 the d[illegible]ing as set out in Table 4 After another four months the tumour exhibited distinct regression and its site was now occupied by gelatinous translucent tissue pervaded by dilated vessels Appearances of this type may be regarded as a radiation reaction to be expected from the doses in question The patient was seen in August 1963 when the translucent tissue had disappeared No tumour was evident

It may just be mentioned that a patient with a centrally located malignant melanoma in the remaining eye (the other eye had been traumatically injured at work) has been treated in the same manner as in Case 4 without showing any signs of recurrence during the year that has elapsed

## Conclusions

It is apparent from these case reports that the modified $^{60}$Co applicator induces retrogression and even disappearance of the malignant tissue. One of the cases has been followed for 34 months and another for approximately 20 months. On account of the small number of cases treated, and the limited period they have been observed, it would be unwise to draw any conclusions regarding the effectiveness of the treatment. Yet, with due consideration to the fact that it embodies the same fundamental principles as STALLARD's $^{60}$Co applicators, the method can be hoped to yield no less favourable results. The method possesses some advantages over STALLARD's technique — predominantly in offering superior application accuracy and shorter anaesthesia — and there would appear to be some justification in recommending it as a complement to other procedures used in the treatment of retinoblastoma.

## SUMMARY

A modified $^{60}$Co applicator embodying the same fundamental principles as the $^{60}$Co Stallard applicators for the treatment of retinoblastomata is described. Five cases are reported.

## ZUSAMMENFASSUNG

Ein modifizierter $^{60}$Co-Applikator, der nach denselben Prinzipien wie der Stallard-$^{60}$Co-Applikator gebaut ist, wurde für die Behandlung von Retinoblastomen angefertigt. Fünf Fälle werden beschrieben.

## RÉSUMÉ

Les auteurs décrivent une modification de l'applicateur de $^{60}$Co de Stallard comportant les mêmes principes fondamentaux pour le traitement du rétinoblastome. Présentation de cinq cas.

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# WHOLE BODY AUTORADIOGRAPHIC STUDIES OF THE DISTRIBUTION OF SULPHUR 35 LABELLED MUSTARD GAS IN MICE

by

C. J. CLEMEDSON, H. KRISTOFFERSSON, B. SORBO and S. ULLBERG

Extensive studies of the biochemical and pathologic effects of mustard gas ($\beta\beta'$ dichlorodiethyl sulphide) were carried out both in the USA (see e.g. GILMAN & CATELL 1948) and in England (see Biochemical Reactions of Chemical Warfare Agents 1948) during and after the second world war, and the essential action of this agent on biologically important compounds is now known. It has thus been found to react with purines, imidazoles, pyrimidines (WHEELER, MORROW & SKIPPER 1955), proteins (see e.g. BOURSNELL 1948) and nucleic acids (see e.g. BERENBLUM & SCHOENTAL 1947, BROOKES & LAWLEY 1960) as well as enzymes (see e.g. NEEDHAM 1948).

Liquid mustard gas rapidly penetrates the human skin and reacts with various cell constituents to produce the well known changes of erythema, vesiculation or necrosis, depending on the dose applied. Rapid penetration of the skin also occurs in animals but the reaction is different from that in human subjects and the effect also varies in different animal species. It has

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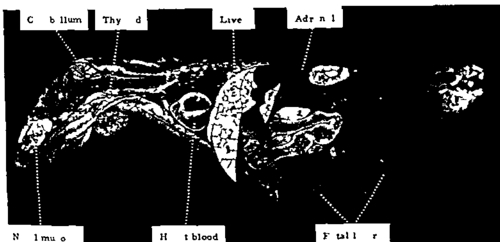


Fig 1 Distribution of $^{35}$S-mustard gas in a pregnant mouse 5 min after intravenous injection White areas correspond to high radioactivity fairly even distribution throughout the body but an accumulation is evident in the kidneys and liver and especially in the nasal region activity in the brain and fetuses

been demonstrated (AXELROD & HAMILTON 1947 CULLUMBINE 1954) that only about 12 per cent of the mustard gas penetrating the skin remains in situ the rest passes rapidly into the circulation

The fate of the mustard gas that is taken up by the blood is not known in detail The content of $\beta\beta$ dichlorodiethyl sulphide or its degradation products has been determined in certain organs (BOURSNELL COHEN et coll 1946 BOURSNELL FRANCIS et coll 1946) but the overall distribution of the agent after systemic resorption is not known As mustard gas also has strong radio mimetic properties a study of its concentration in various parts of the body is of further interest The aim of the present investigation was to study the general distribution of $^{35}$S labelled $\beta\beta$ dichlorodiethyl sulphide after its cutaneous and intravenous administration in mice

*Methods* $^{35}$S labelled $\beta\beta$ dichlorodiethyl sulphide with a specific activity of 189 mC/g was obtained from the Radiochemical Centre Amersham England The mustard gas was diluted with propylene glycol (10 mg dichlorodiethyl sulphide in 1 5 ml propylene glycol) Eighteen adult mice 15 males and 3 pregnant females weighing about 20 g were used for the experiments

The mustard gas was administered cutaneously to nine animals all males The animals were thoroughly clipped and shaved on a small area on the back and about 1 mg of the diluted mustard gas was applied to this area by means of a fine glass rod The diluted mustard gas in a dose of 0 20 ml per animal was administered intravenously into a tail vein in the remaining nine animals The animals were killed at various intervals by immersion in a mixture of solid

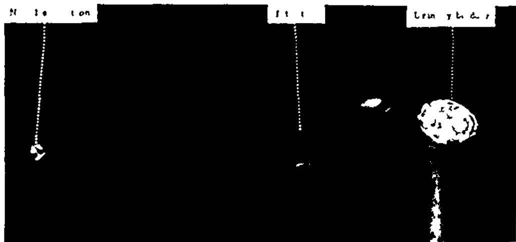


Fig. 2. Distribution of $^{35}$S-mustard gas in a pregnant mouse 1 hour after intravenous injection. Radioactivity now nearly completely excreted with exception of that in the nasal region, intestines, kidneys and bladder

carbon dioxide and acetone (— 78 C) The animals were sacrificed at the following times cutaneous administration group 15 min, 1 hour, 4 hours, 1 day and 4 days after the administration, intravenous administration group 5 min 15 min 1 hour, 2 hours and 4 hours after the injection

The frozen animals were sectioned and autoradiograms prepared according to the method developed by ULLBERG (1954, 1958) for autoradiography of small laboratory animals Sagittal sections, 20 $\mu$ thick, through the whole animal were made at different levels and the sections were then dehydrated at — 10 C Gevaert Dentus Rapid film was employed for all the autoradiograms (exposure time 32 days in all experiments)

## Results

*Intravenous administration* The $^{35}$S mustard gas was rapidly taken up from the blood stream when administered intravenously The radioactive isotope was fairly evenly distributed throughout the body with a significant accumulation appearing mainly in the liver and kidneys and especially in the nasal region at all times studied The passage was apparently free to the brain and the isotope also rapidly passed the placenta

A somewhat higher activity than in the blood was evident in a number of organs as early as 5 min after the injection of the compound (Fig 1) The highest content of radioactivity was present in the nasal region followed by the kidneys liver, intestines and salivary glands The central nervous system showed evidence of a fairly high uptake with an even distribution of the activity but with some predominance in the granular layer of the cerebellum A slight accumulation was also evident in the walls of larger arteries and in

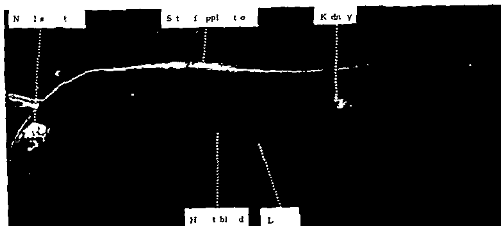


Fig 3 Distribution of S mustard gas in a mouse 15 min after administration to the skin Rapid uptake in the nasal region

the thyroid gland The activity was very evenly distributed in the rest of the body and the lymph nodes spleen thymus pancreas suprarenals pituitary gland and bone marrow all presented about the same activity as the skeletal muscles The concentration of the isotope was low in the hard tissues, such as the bone and teeth as well as in the cartilages

The radioactivity disappeared quickly from most of the tissues except from the nasal region the biliary ducts and urinary tract The activity was very low in most tissues as early as 1 hour (see Fig 2), 4 hours after the administration of the radioactive mustard gas hardly any activity was detectable

The fetuses had also taken up radioactivity, although the concentration in their tissues were lower than in those of the dam The distribution pattern however, was about the same in the fetus as in the dam

In an attempt to determine whether the radioactivity in the nasal region was also present in the secretion labelled mustard gas was given intravenously in two rats (dose 20 mg/kg bodyweight) The animals were then decapitated 15 min after injection and the nasal cavity was washed out with 10 ml saline The *washing solution was radioactive but its total activity corresponded only* to 0 01 and 0 025 per cent respectively, of the dose injected in each animal These figures appeared to be low when compared to the relatively high activity localized to the nasal regions in the autoradiograms but this may have been due to difficulties in removing the nasal secretion by the washing procedure used

*Cutaneous administration* The $^{35}$S mustard gas applied to the skin was rapidly absorbed and as early as 15 min after the administration activity was found in various body tissues and organs of the animals (Fig 3) The distribution

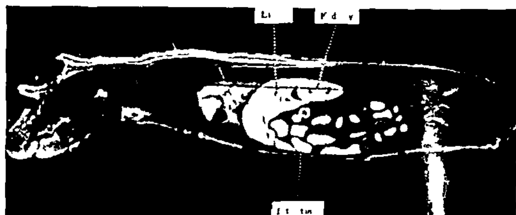


Fig. 4. Distribution of $^{35}$S-mustard gas in a mouse 4 hours after administration to skin. Marked accumulation present in the kidneys, liver and intestines.

pattern was essentially the same as that obtained after the intravenous administration of the compound. Thus, even in these animals the highest concentration was present in the excretory organs.

The high activity evident in the blood after the intravenous injection of the labelled compound was never encountered after its cutaneous application. On the other hand, it was found that significant amounts of the isotope remained in the body for a much longer time after cutaneous than after intravenous administration (see Figs. 4 and 5). This was probably due to a slow continuous uptake of mustard gas or its degradation products from the skin. Thus, even 4 days after administration there was still a considerable amount of activity in the nasal region as well as in the intestines and bladder (Fig. 5), and the skin at the site of the application also retained a fair amount of the isotope.

## Discussion

The results of the present investigation are largely in agreement with those of BOURSNELL et coll. (1946) who measured the $^{35}$S activity in various dissected organs of rabbits, after the intravenous administration of labelled mustard gas. These authors, however, reported a comparatively high activity in the lungs, the activity being of the same magnitude as that present in the liver; this is in contrast to the fairly low activity apparent in the lungs in the present study. It is of interest in this connection to note that DAVISON et coll. (1961) reported only traces of radioactivity in the expired air of rats that had been given radioactive sulphur mustard gas. On the other hand, a comparatively high activity was found in the central nervous system in the present investigation, whereas BOURSNELL et coll. measured only a fairly low activity in the brain in their experiments. This divergence in results may be due to the different techniques used and possibly also to species differences.

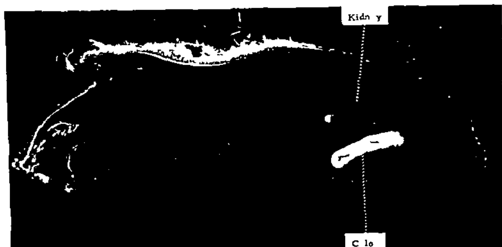



Fig 5 Distribution of $^{35}$S mustard gas in a mouse 4 days after administration to the skin Some radioactivity still remains at the site of application

Since the whole body autoradiography method used allows rapid screening of almost all body tissues, accumulation of the radioisotope may be observed also at unexpected sites in the body Thus, the high content present in the nasal region would probably have escaped detection if measurements had been made only on dissected tissues

The radioactivity observed in the various organs and tissues in this study must be present as degradation products of the mustard gas and not as the parent compound itself (see e g BOURSNELL et coll 1946 and BOURSNELL 1948) as sulphur mustard gas is rapidly converted in vivo to degradation compounds of which thiodiglycol bis $\beta$ chloroethyl sulphone and the conjugate with glutathione are the most important (DAVISON et coll 1961) It would have been of interest to identify these metabolites in the different tissues but this was beyond the limits of the present investigation

## SUMMARY

$^{35}$S labelled sulphur mustard gas was applied to the skin of mice and also given by intravenous injection the distribution of the radioactivity being followed by whole body autoradiography A high uptake was found in the kidneys and liver the nasal region rapidly accumulated a high activity and considerable activity was also evident in the central nervous system Some experiments in pregnant animals demonstrated a passage of radioactivity to the fetuses

## ZUSAMMENFASSUNG

Schwefelsenfgas das mit $^{35}$S markiert war wurde auf die Haut von Mausen aufgestrichen und ebenfalls intravenos eingespritzt Die Verteilung der radioaktiven Substanz wurde mittels Autoradiographie des ganzen Körpers studiert Die Hauptaufspeicherung fand sich in den Nieren und der Leber die Nasenregion zeigte bald eine rasch steigende Aktivitat und beträchtliche Aktivitat wurde auch im Zentralnervensystem gefunden Versuche an schwangeren Tieren zeigten einen Übergang der Aktivitat in die Embryonen

## RÉSUMÉ

Les auteurs ont appliqué sur la peau et aussi administré par voie intraveineuse à des souris une ypérite soufrée marquée au $^{35}S$ et ont étudié par autoradiographie de tout le corps la distribution de sa radioactivité Ils ont constaté une fixation élevée dans les reins et le foie la région nasale fixe rapidement une activité élevée ainsi que le système nerveux central Certaines expériences sur des animaux gravides ont montré un passage de la radioactivité dans les foetus


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FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL), UNIVERSITY OF CAMBRIDGE, AND THE RADIOTHERAPEUTIC CENTRE, ADDENBROOKE'S HOSPITAL, CAMBRIDGE, ENGLAND

# INVESTIGATION OF A RADIOACTIVE DRUG (TRA 119) WITH SPECIAL REFERENCE TO AUTORADIOGRAPHIC AND RELATED STUDIES

by

J S MITCHELL E A KING, D H MARRIAN and BARBARA CHIPPERFIELD

An attempt is being made by a team at Addenbrooke s Hospital Cambridge to develop a radioactive drug for the purpose of selective internal therapeutic irradiation in the treatment of patients with cancer This approach is based on the assumption that sufficiently large biochemical differences exist between malignant cells and normal cells to make it possible to devise organic compounds which are concentrated or absorbed to some extent selectively by the cells of certain malignant tumours and carry incorporated radioactive atoms with high specific activity Despite the great difficulties the possibility may be en visaged that a suitable radioactive drug could be curative since ionizing radiations are the only agents apart from surgery which as yet have cured substantial numbers of patients with cancer

Tritium appears to be the most promising radioactive isotope for this applica tion Most of our investigations have concerned tritiated derivatives of 2 methyl 1 4 naphthaquinol bis (disodium phosphate) — Synkavit (Roche Products) our compound I This compound, which has been investigated since 1946 as a

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therapeutic radiosensitizer was found unexpectedly to concentrate to some extent selectively in the malignant cells of some human and animal tumours (MITCHELL 1960) Studies of the distribution and selective concentration of compound I in the tumour and other tissues have been made, using the methods of fluorescence with Wood's light (MITCHELL 1949, 1953) and radioactive labelling with $^{14}$C, $^{82}$Br and $^{131}$I (MARRIAN and MAXWELL, 1956 a and b, MAXWELL 1954 1955) and with tritium (see MARRIAN 1957)

We have investigated the use of tritiated compound I in the treatment of patients with advanced malignant disease since February 1959 A number of accounts of various aspects of the laboratory and clinical investigations have been published (HORWITZ et coll 1959, MARRIAN et coll 1961 SIMON REUSS 1961 MITCHELL 1961, 1962 CHIPPERFIELD and MARRIAN 1962) Information of great value from the point of view of the clinical applications in man was obtained in studies of the treatment of spontaneous malignant tumours and leukaemias in cats and dogs (SILVER et coll 1962) It is of interest that preparations of tritiated compound I (TRA 72) *produced mutations in the cruciferous plant Arabidopsis thaliana*, similar to those produced by roentgen rays McKELVIE 1962)

In the attempts to treat patients the preparations of tritiated compound I have been administered by *some form of intra arterial injection whenever possible* otherwise by intravenous injection In the treatment of the first 27 patients we used material tritiated by the Wilzbach exchange method but this contained incorporated tritium at only relatively low levels of specific activity together with varying amounts of tritiated water

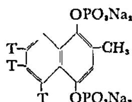
Then one of us (D H M ) devised a method of tritiation which made it possible to obtain reliable preparations of the compound containing approximately one atom of tritium per molecule with the tritium firmly bound This compound 2 methyl-6-tritio-1 4-naphthaquinol bis-(disodium phosphate) was prepared in collaboration with Roche Products, Welwyn Garden City and the Radiochemical Centre Amersham (ANDREWS et coll 1962) The material used was prepared by the Radiochemical Centre Amersham accordingly we have found it convenient to describe it by the code designation in the catalogue of the Radiochemical Centre TRA 72

We have investigated TRA 72 in the treatment of 21 patients who were seriously ill with advanced recurrent radioresistant or refractory malignant disease Temporary improvement assessed on the basis of observation of some form of definite objective improvement and/or striking relief of pain as indicated by a great reduction of the analgesics required in particular discontinuance of the need for morphia was observed in 5 of these 21 cases there was *probably some improvement attributable to the treatment in* a further 4 cases It appeared that under the conditions of this trial definite though small palliative effects were observed it seemed likely that these were associated with the relatively low levels of radiation dose delivered by the radioactive drug

Extensive measurements of the specific activity of tritium in biopsy and autopsy specimens provided evidence for some degree of selective concentration of the compound in certain human malignant tumours in relation to the bone marrow after both intra arterial and intravenous administration The specific activity of the specimens of tumour was almost invariably higher than that of specimens of bone marrow and of skeletal muscle often by a factor of 3 and sometimes by a factor of 6 to 7 The values of the specific activity observed were such that it appeared that at least three atoms of tritium per molecule of compound I are neces

sary to make it possible to deliver doses of radiation within the therapeutic range to tumours with adequate uptake and a sufficiently high radiosensitivity

The required drug 2 methyl 5 6 7 tritio 1 4 naphthaquinol bis (disodium phosphate) has been prepared as a result of a collaborative effort by the Department of Radiotherapeutics University of Cambridge the Radiochemical Centre Amersham and Roche Products Welwyn Garden City (ANDREWS et coll 1962) Its formula is given below




The preparations used will be referred to as TRA 119 again following the code of the catalogue of the Radiochemical Centre

During the last year we have carried out clinical and laboratory investigations of TRA 119 both to study its therapeutic possibilities and to obtain information necessary for widening the scope of its application and for the further development of radioactive drugs generally So far TRA 119 has been used in the treatment of 33 patients with advanced and recurrent malignant disease when conventional methods of treatment were not likely to help

The main aim of this paper is to consider the evidence for selective concentration of TRA 119 in the malignant cells of some tumours after intravenous and intra arterial injection, and to try to relate the concentrations of tritium observed in the malignant cells and normal cells to the therapeutic effects on the basis of some form of dosimetry

As with TRA 72 many measurements have been made of the specific activity of specimens of tumours and normal tissues obtained by biopsy surgery and autopsy after the administration of TRA 119 Following usual procedures, these macroscopic average values of the specific activity can be utilized for *approximate calculation of the* average doses of radiation delivered, *on the* basis of a number of assumptions of which the most important is that the radioactive material is uniformly distributed However the distribution of tritium is almost invariably non uniform both within the cells and in the tissues Accordingly the calculated values of the macroscopic average doses although of some interest cannot be expected to give reliable or detailed information concerning the effective doses of radiation delivered in many tissues and especially in the case of malignant tumours where a variable and often substantial proportion of the volume of tissue is occupied by stroma — quite apart from the variability of the malignant cells themselves

The use of a radioactive drug makes it necessary to study radiation dosimetry at the microscopic level and to try to evaluate the cell dose with the appropriate time factors For this purpose, autoradiographic studies have been carried out as an essential part of the investigation of TRA 119 So far it has not been possible to use these autoradiographs for quantitative cell dosimetry However

**Table 1**

*Cases treated by means of TRA 119 between 7.3.1962 and 17.12.1962 (all cases confirmed by histological examination)*

| Diagnosis | Number of cases Total | Intra-arterial route | Intravenous route |
|---|---|---|---|
| Carcinoma of gastro-intestinal tract (stomach, caecum, colon and rectum) adenocarcinoma, recurrent and advanced | 7 | 4 | 3 |
| Advanced cerebral glioma in conjunction with surgery | 8 | 8 | 0 |
| Carcinoma mammae advanced and recurrent | 3 | 0 | 3 |
| Malignant melanoma of skin, recurrent | 3 | 1 | 2 |
| Carcinoma of skin, advanced and recurrent | 2 | 1 | 1 |
| Carcinoma of head of pancreas with extensive metastases | 2 | 0 | 2 |
| Metastases in liver — adenocarcinoma, but no primary found | 1 | 0 | 1 |
| Hodgkin's disease, advanced with generalised pruritus | 1 | 0 | 1 |
| Mycosis fungoides, advanced after much radiotherapy | 1 | 0 | 1 |
| Neuroblastoma, advanced | 1 | 0 | 1 |
| Seminoma of testis, advanced and recurrent | 1 | 0 | 1 |
| Carcinoma of Fallopian tube, metastases after surgery and radiotherapy | 1 | 0 | 1 |
| Secondary carcinoma in R. femur, primary uncertain | 1 | 1 | 0 |
| Reticulum cell sarcoma of bone, with extensive metastases | 1 | 0 | 1 |
| Total numbers | 33 | 1 | 18 |

the qualitative and semi-quantitative autoradiographic findings taken in conjunction with the measured values of the macroscopic specific activity appear to give useful information.

*Some clinical aspects.* The selection of patients for the investigation of the therapeutic possibilities of TRA 119 presents many problems. So far we have felt compelled to follow the general principles of selection of patients which we used for the studies of TRA 72 (see MARRIAN, MARSHALL and MITCHELL 1961, p. 286). The cases which have been treated may be classified in the following main groups:

1. Late cases, where no form of conventional treatment is likely to be able to offer further help, i.e. with advanced, recurrent, radioresistant and refractory tumours.
2. Earlier, in the sense of somewhat less advanced, but otherwise untreatable cases.
3. Advanced cases of highly radiosensitive malignant tumours and allied diseases.

The cases treated by means of TRA 119 between 7.3.1962 and 17.12.1962 are summarised in Table 1. The previous studies with TRA 72 suggested that particular attention should be paid to adenocarcinoma of the gastrointestinal

tract malignant melanoma, advanced carcinoma of the skin and the highly radiosensitive malignant diseases Of particular interest is the study of advanced cerebral glioma which is being carried out in collaboration with Mr Walpole Lewin and Dr T D Hawkins and will be the subject of a separate report

In addition to the cases listed in Table 1, so far 4 cases of carcinoma of the bronchus have been investigated by means of pre operative injections (three intravenously and one into the pulmonary artery) with subtherapeutic doses of TRA 119

In Table 2 is summarised some more detailed information about 6 cases, which were selected because of the type of disease and the availability of biopsy specimens for which autoradiographs showed uptake of TRA 119 into tumour cells and in which measurements of the specific activity have been made

The results of measurements of the specific activity of autopsy specimens in one of the cases 14 days after intra arterial injection of the dose of 10 8 curies of TRA 119 which is one of the largest single doses administered so far, are recorded in Table 3 in this case intra arterial injection was made through a catheter into the external carotid artery which had been exposed surgically

Evidence will be discussed for two other cases in which apparently satis factory autoradiographs showed no evidence of uptake into the tumour cells Further it is of interest that there were 6 cases in which single intravenous doses of between 9 6 and 10 9 curies of TRA 119 were administered only one of these a case of carcinoma of the head of the pancreas with extensive metas tases in bones showed evidence of a serious fall in the level of blood platelets with petechial haemorrhages This example appears to have been the only serious toxic effect attributable to TRA 119 in this series of 33 cases In a few cases where the amount of TRA 119 given corresponded to more than 75 mg of compound vasomotor reactions were observed but these were never serious

It is of course too early to draw any general conclusions about the possible therapeutic value of TRA 119 and great caution is necessary (For a discussion of the methods of assessment see MARRIAN MARSHALL and MITCHELL 1961 ) At present, it can be reported that there was useful relief of pain in 6 out of 9 cases in which pain was a serious problem and in one case of Hodgkin s disease generalised pruritus was relieved after a single intravenous dose of 2 9 curies Moreover in Case 52 (see Table 2) there appeared to be delayed retrogression of metastatic nodules of melanoma after three intra arterial injections of TRA 119

The procedures for intra arterial injection of TRA 119 and the methods used have been described (HORWITZ et coll 1959 GREGG 1960 MARRIAN, MARSHALL and MITCHELL 1961 p 287) In general a preliminary arteriogram is carried out Tolazoline (Priscol) has been used in many cases before the intra arterial injection of TRA 119 Although the general policy has been to give a single intra arterial injection of TRA 119 an attempt is being made in some cases to repeat the intra arterial injection after an interval of between 10

**Table 2**

*Details of selected cases treated by TRA 119 (* indicates that autoradiographs of part of the specimen*

| Case No | Disease and previous treatment | Age in years sex and weight | Route of injection and date | Amount of TRA 119 injected | |
|---|---|---|---|---|---|
| | | | | Curies | mg |
| 49 | Metastases in anterior abdominal wall Ca rectum adenocarcinoma abdominal perineal resection 1 1 59 | 66<br>M<br>51 kg | IV<br>7 3 62 | 1 4 | 8 |
| | | | IV<br>4 5 62 | 1 5 | 16 5 |
| | | | IV<br>29 5 62 | 4 | 16.5 |
| | | | Died<br>11 10 62 | | |
| 57 | Metastases of malignant melanoma of skin multiple recurrent nodules of R leg below knee mole removed 5 8 53 re-excision of primary site and block dissection of inguinal nodes (not involved) 10 9 53 excision of recurrent nodules 18 4 59 and in September 1960 | 46<br>F<br>55 kg | IV<br>19 4 62 | 1 | 7.3 |
| | | | IV<br>1 6 62 | 4 0 | 21 |
| | | | IV<br>4 7 62 | 9 8 | 74 |
| 66 | Fungating metastases of anterior abdominal wall advanced recurrent Ca caecum — adenocarcinoma hemicolectomy and side to-side anastomosis 18 9 62 laparotomy and excision of recurrent tumour March 1962 post-operative Endoxan | 37<br>F<br>54 kg | IV<br>30 7 62 | 5 2 | 34 5 |
| | | | IV<br>17 8 62 | 9 9 | 69 |

*are shown in the figures)*

| Specimen and time after injection | Specific activity of specimen (μC per gram of wet tissue) | | Clinical response and other information |
|---|---|---|---|
| | Tumour | Other specimens | |
| Biopsy 30 min | *28 3 (± 1 ) | Adjacent muscle 15 5 (± 1 ) | Slowly growing well-differentiated tumour with grossly fibrotic stroma |
| | | | Relief of pain after first injection no objective evidence of tumour inhibition |
| — | | | |
| — | | | |
| Autopsy | *2 58 (± 2 ) | | |
| Biopsy 30 min | 74 3 (± 13 ) | Muscle 27 8 (± 6 ) | Good general condition no evidence of extension of the tumour outside the R leg below the knee sternal marrow normal 28 6 6? |
| 30 min | | Peripheral blood 72 ± 1 ) | Compression of vessels and withdrawal of effluent blood from limb |
| — | | | Appeared to have late retrogression of nodules 16 11 62 including new nodules which had developed since injections |
| Biopsy nodule near ankle 41 min | *84 2 (± 2 ) | | |
| Nodule near knee 46 min | 80 4 ± 2 ) | | |
| 1 hour | | Peripheral blood 78 (± 4 ) | |
| Biopsy 30 min | 95 (± 3 4 ) | | Very ill and grossly anaemic requiring transfusion no evidence of tumour inhibition |
| 30 min | 300 (± 1 ) | | |
| 7 days | 8 8 (± 3 5 ) | | Died 15 9 62 |

Table 2 *(cont)*

| Case No | Disease and previous treatment | Age in years sex and weight | Route of injection and date | Amount of TRA 119 injected | |
|---|---|---|---|---|---|
| | | | | Curies | mg |
| 71 | Extensive recurrent squamous carcinoma of L. pinna involving side of head and neck original excision 11 1 62 further surgery on 22 2 62 and 4 4 62 and radical Co 137 teletherapy 7 5 62 to 8 6 62 | 66 M 47 kg | IA 6 9 62 Died 20 9 62 | 10 8 | 54 |
| 80 | Recurrent nodules on chest wall spheroidal-celled carcinoma and axillary nodes Ca mammae R stage III recurrences after roentgen therapy 29 5 61—16 6 61 simple mastectomy 12 1 62 and local roentgen therapy 16 4 62 and 14 6 62 no response to Durabolin | 59 F 101 kg | IV 9 11 62 | 10 1 | 73 5 |
| 86 | Recurrent mass in L. ischiorectal fossa and perineum Ca rectum adenocarcinoma abdomino-perineal excision 16 5 62 | 53 F 67 5 kg | IV 4 12 62 | 9 7 | 57 4 |

days and 4 weeks For both intravenous and intra arterial routes of administration, it is considered important to inject the TRA 119 as rapidly as possible in order to minimise its reaction with SH compounds in the blood and to make certain that as high a proportion as possible reaches the tumour cells

*Preparations of TRA 119 used* The compound 2 methyl 5 6 7 tritrio-1 4 naphthaquinol bis (disodium phosphate) corresponds to a specific activity of 87 3 curies per mM accordingly 1 curie is contained in 4 88 mg of compound

The TRA 119 is prepared by the Radiochemical Centre Amersham in batches which usually contain between 10 and 30 curies The specific activity of the different batches has varied considerably and was usually between 50 and 80 curies per mM

It is interesting that the use of batch No 5 which had the theoretical value of 87 curies per mM corresponding to 3 atoms of tritium per molecule gave high values of the uptake into

**Table 2** *(cont )*

| Specimen and time after injection | Specific activity of specimen ($\mu$C per gram of wet tissue) | | Clinical response and other information |
|---|---|---|---|
| | Tumour | Other specimens | |
| Biopsy 30 min | Anterior part 8 990 (± 2 7 ) | Peripheral blood 399 (± 1 7 ) | Deteriorated and died with severe bronchopneumonia at autopsy (Dr R W Ainsworth) carcinoma cells show severe degenerative changes with conspicuous vacuolation of their cytoplasm |
| 3 / hours | Anterior part 378 (± 2 6 ) | | |
| | *Posterior part 1 81ↄ (± 3 8 ) | | |
| Autopsy | 40 3 (± 5° ) | (See Table 3) | |
| Biopsy skin nodule 35 min | *102 5 (± 1 ) | | Complete relief of pain but objectively no improvement |
| Biopsy Perineal recurrence 30 min | *2 8 (± 4 ) | | Pain relieved temporarily but no objective improvement |

specimens of tumour per curie injected in a recurrent cerebral glioma (Case 50) and a metastatic nodule of malignant melanoma (Case 52 first injection) though there was not a high uptake in a biopsy specimen of primary carcinoma of the rectum (Case 51) There appears to be some association between the values of the specific activity of the preparation of TRA 119 used and of the uptake into biopsy specimens of tumour defined in terms of microcuries per gram per curie injected but there is obviously considerable variation between the uptake of the tumours in different patients The highest values of the uptake observed so far were in Case 71 (see Table 2) after intra arterial injection of a preparation (batch No 20) of specific activity 62 curies per mM The limited evidence available confirms that the uptake into tumour biopsy specimens is usually higher with the preparations of TRA 119 of specific activity in the range between 60–87 curies per mM than with preparations of TRA 72 of a specific activity of between 16 and 29 curies per mM

The solutions of TRA 119 are sterilised by filtration into sterile rubber-capped bottles Chlorocresol is added as a bacteriostatic to give a concentration of 0 2 % The solutions are

**Table 3**

*Specific activity of autopsy specimens (Case No 71) 14 days after intra arterial injection of 10.8 curies of TRA 119 into the exposed left external carotid artery through a catheter and after arteriography and a further injection of Priscol (body weight 47 kilograms)*

| Tissue | μC per gram of wet tissue | Tissue | μC per gram of wet tissue |
|---|---|---|---|
| *Tumour* | 40.25 ± 5 | Skeletal muscle | 7.5 ± 5 |
| Bone marrow | 10.2 ± 4* | Cardiac muscle | 13.7 ± 1 |
| Kidney | 42.1 ± 1*$_o$ | Lung | 11.2 ± 1 |
| Small intestine | 20.1 ± 2 | Testis | 21.7 ± 3* |
| Spleen | 13.0 ± 3 $_o$ | Brain — right temporal lobe | 10.9 ± 2 |
| Liver | 15.9 ± 2 | Brain — left temporal lobe | 10.4 ± 4 |
| Pancreas | 13.7 ± 17 | | 11.4 ± 5 |

frozen immediately delivered in containers surrounded by solid $CO_2$ and kept at −78 C surrounded by solid $CO_2$ in a Dewar vessel in a deep freeze at ambient temperature about −20 C.

Each batch of TRA 119 is tested biologically before the clinical use by the two methods

1 To exclude the possibility of acute toxicity by intravenous injection into a rabbit in doses corresponding at first to 11 curies per 70 kg of body weight and later to 22 curies per 70 kg No acute toxic effects have ever been encountered The rabbits are being kept for the rest of their life span under observation with regular blood counts for which we are indebted to Mr R. Flemans Full autopsy studies are planned

2 Studies on tissue cultures mainly of HeLa cells, to check sterility and to demonstrate the uptake of TRA 119 into the tumour cells under standard conditions by means of autoradiography (see SIMON REUSS 1961)

The difficulties raised by the decomposition of TRA 119 in aqueous solution as a result of autoirradiation has been overcome to a large extent by the low temperature storage Nevertheless, despite this deterioration of the material occurs in the frozen solution The problems of radiation stability and chemical purity are being investigated by our colleagues at the Radiochemical Centre Amersham From the biological point of view by means of the autoradiographic studies on tissue cultures Mrs Simon Reuss has found that many batches show no substantial decrease in the labelling of the tumour cells with only a little increase in back ground after two weeks though some batches deteriorate more quickly Accordingly it is considered that good batches can be used for up to two weeks and perhaps even up to three weeks An account of these studies will be published separately

*Measurement of specific activity of specimens of tissue* For routine assay of tritium the tritiated water obtained by combustion of specimens of tissue of weight 10 to 40 mg has been counted in a Nuclear Enterprises NE 8301 liquid scintillation counter using either NE 213 scintillator or SP2 (Nash and Thompson Ltd Chessington Surrey) (See MARRIAN MARSHALL and MITCHELL 1961 p 282 ) The efficiency of the counter was checked regularly by counting a sample of tritiated water of known specific activity At first the weighed specimen of tissue was sealed into a hard glass tube (M J N combustion tubing) together with copper oxide and reduced copper and heated at 650 for 6 hours (JACOBSON et coll 1960) the water formed was sublimed in vacuo into a vial and kept for counting More recently the tissues have been burned in a flask of oxygen (SCHONIGER 1955 1956) containing a known volume of water as scavenger Aliquots of water were then counted as before

*Histologic and autoradiographic techniques* At first the specimens of tissue were fixed in Susa and the sections stained with Ehrlich s haematoxylin (see Fig 1) It appeared that diffusion

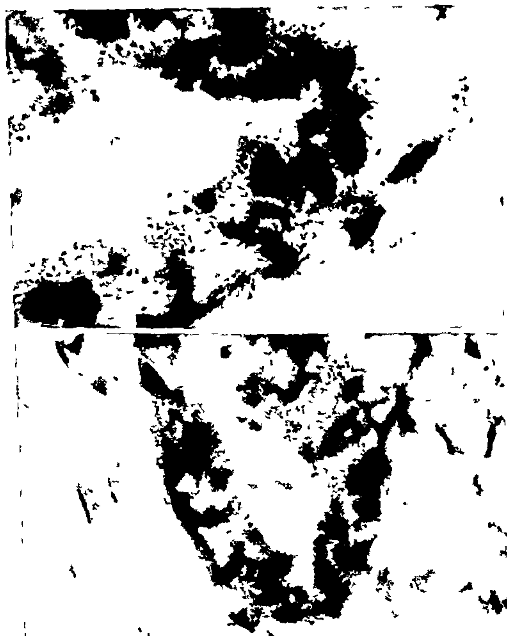


Fig 1 Case 49 Sections of metastases of adenocarcinoma of rectum. Autoradiographs of biopsy specimen upper view × 1 750 lower view × 1 050

of the radioactive material in the specimens of tumour was a problem and it became necessary to use a freeze-drying preparation of the tissues. In general standard procedures have been followed. The specimens of tissue were frozen as quickly as possible after removal by plumping into liquid isopentane cooled with liquid nitrogen. Vacuum dehydration of fragments of dimensions of about 5 mm was carried out at temperatures between −30 and −50° C for 5 days and was followed by embedding in degassed paraffin wax under vacuum. Sections were cut at thickness 5 μ selected as corresponding to a layer of infinite thickness in relation to the range of the beta particles of tritium (see ROBERTSON and HUGHES 1959). Autoradiographs were prepared with $G_5$ liquid emulsion (Ilford) with exposure times at 3° C between 12 hours and 10 days according to the specific activity. ID 19b developer (Ilford) for 10 minutes, then fixation, washing in distilled water and immersion in 70 per cent alcohol at 3° C and Feulgen staining.

## Dosimetric considerations

As a preliminary to consideration of the results of measurement of the specific activity of the specimens of tissues and of the evidence provided by the autoradiographs, it is necessary to summarise the relevant physical properties of tritium and the calculations of the dose of radiation delivered (see MARRIAN, MARSHALL and MITCHELL 1961, MITCHELL 1962).

The best value of the mean energy of the beta particles of tritium is 5.73 ± 0.03 keV, corresponding to the half life 12.43 ± 0.04 years (PILLINGER, HENTGES and BLAIR 1961).

The range in unit density tissue corresponding to the mean energy of the beta particles of tritium is approximately 1 μ. The maximum energy of the beta particles is 18.7 ± 0.1 keV, so that the corresponding maximum range is approximately 6 μ.

Calculations of the radiation dose rates and isodose curves about a point source of tritium in unit density tissue have been published (ROBERTSON and HUGHES 1959, ROBERTSON, BOND and CRONKITE 1959, KUNKEL 1962). Radiation dose calculations in cells containing intranuclear tritium have been made (GOODHEART 1961, KUNKEL 1962).

The linear energy transfer for the beta particles of mean energy has the value of ca 4 keV per μ, near the end of the track, the value of the linear energy rises to about 6 keV per μ.

On the basis of a value of the mean energy of the beta particles of tritium of 5.73 keV and with the assumption of uniform distribution of the radioactive material, approximate calculations have been made of the macroscopic average values of the dose delivered by tritium from the point of view of its therapeutic applications. 1 mC tritium per gram of tissue delivers a dose of 293 rad in 24 hours. Other results are given in Table 4 (see also MITCHELL 1962). A brief discussion is necessary to consider the implications of the numerical values.

The limited evidence available, mainly from the studies of TRA 72, concerning the values of the biologic half life of the tritium in tumours and normal tissues has been discussed elsewhere (see MARRIAN, MARSHALL and MITCHELL 1961). It appears that the value of the main biologic half life (B.H.L.) is in the

**Table 4**

*Dosimetry of tritium in therapeutic applications (approximate dose delivered by one curie of tritium administered to a 70 kg patient)*

| Biologic half life | 3 days | 6 days | 9 days | 12 days | 13 days |
|---|---|---|---|---|---|
| Calculated value of total dose delivered | 18 12 rad | 36.2 rad | 54 4 rad | 72 5 rad | 78 5 rad |
| Mean l fe | 4 33 days | 8.66 days | 13 0 days | 17 3 days | 18 8 days |
| Time factor assumed for calculation of the equivalent single acute dose (see Mitchell 1960 p 234) | 2 22 | 2 54 | 2 64 | 2 69 | 2 71 |
| Approximate equivalent single dose delivered at high dose rate | 8 2<br>say 8 rad | 14 3<br>say 14 rad | 20 6<br>say 21 rad | 26 9<br>say 27 rad | 29 0<br>29 rad |
| Approximate biologically equivalent single dose of Co gamma radiation (R. B E = 1 7) | 14 r | 24 r | 35 r | 46 r | 50 r |

These calculations assume uniform distribution of the tritium throughout the body and give the approximate dose for different values of the biologic half life

region of 13 days for a number of different tumours though values as low as about 3 to 4 days have been observed, for case No 66 treated with TRA 119 the findings are consistent with a value of 1 4 days The rapid initial loss of radioactivity from at least some tumours, with a half life of about 8 min in one case needs further investigation The possibility of an additional very long half life must be envisaged for some tumours It is likely that the values of the main biologic half life for many normal tissues including bone marrow, are in the region of 3 to 6 days The apparently higher value in the region of 11 to 12 days found for the small intestine in the autopsy studies also needs further investigation

The best estimate of the relevant value of the relative biologic effectiveness (R B F ) of the tritium beta particles of TRA 119 in relation to Co gamma radiation is 1 7 This value must be regarded as provisional and needs direct experimental investigation from the point of view of therapeutic applications The possibility may be envisaged of somewhat different values of the R B E for TRA 119, tritiated water and tritiated thymidine

It can be deduced from Table 4 as a first approximation that the maximum single amount of TRA 119 which can be administered with safety to the whole body in a patient of weight 70 kg is approximately 11 curies The safety of this amount has been confirmed for patients without serious bone marrow damage It is likely that the calculation involves a safety factor on account of the non uniformity of the macroscopic distribution of the tritium, in addition to the

effects of non uniform distribution of the compound within the cells The size of the safety factor is not yet known but it is necessary to be cautious about this particularly because of the possibility of late effects of the irradiation on the kidney during excretion

In these calculations account must be taken of the differential absorption ratio (D A R ) which is defined as the ratio of the observed radioactivity per gram of tissue to the total injected radioactivity per gram of body weight (cf KENNY, MARINELLI and WOODWARD 1941) Again it is to be noted that the D A R refers to the macroscopic average value

For the administration of 11 curies in a patient of body weight 70 kg the calculations on the basis of Table 4 lead to the following approximate values of the biologically equivalent single dose of $^{60}$Co gamma radiation

for bone marrow with B H I 4 days 190 r
for small intestine with assumed B H I 11 5 days 480 r
for kidney with B H I 6 days and assumed D A R 2 530 r
for tumour with B H I 3 days 150 r, and for B H L 13 days 550 r

In these calculations, the limiting factor was taken to be the threshold for acute radiation effects on the small intestine, it was noted that the threshold dose for the gastro intestinal form of the acute radiation syndrome in man after total body irradiation is given as 500 r (GERSTNER 1958) In fact, after intravenous injection of 9 6 to 10 9 curies in patients of different body weights only slight nausea was observed in one case Further the absence of appreciable haematologic changes in patients with essentially normal bone marrow, together with the crude calculations of the dose received by the kidney, suggest that the safety factor may prove to be about 50 per cent

The calculated doses for tumour are consistent with the striking palliative effects observed after intravenous injection of TRA 119 in some advanced cases of certain highly radiosensitive diseases e g Hodgkin s disease testicular seminoma However to obtain useful therapeutic effects with most malignant tumours, a high D A R is essential It can be assumed that with a single dose of gamma radiation, a minimum tumour dose of about 2 250 r is required to cure a squamous carcinoma of a diameter of about 1 cm Accordingly, the D A R required must be at least about 4 to 15 depending on the B H L , in fact higher values are necessary for more extensive tumours The simplest method of attaining these high values of the D A R appears to be by means of intra arterial injection of the TRA 119, with draining off of the returning venous blood whenever possible With intra arterial injection, the total amount of TRA injected may be limited by the radiosensitivity of the normal tissues concerned, especially the gastro intestinal tract and probably also the brain It seems likely that the time factors are such that radiosensitization by the compound is not important, although this possibility cannot be completely excluded

These admittedly crude calculations are of some interest in that by this method it has been possible to reach a provisional working level of maximum

safe dosage of TRA 119 for administration to the whole body However it must be emphasised that this level has been approached cautiously and empirically and that it may be possible to go to somewhat higher levels such as 16 curies per 70 kg of body weight, in patients with essentially normal bone marrow, when preparations of TRA 119 of the full theoretical specific activity 87 curies per mM become regularly available

The next and apparently most difficult step is to relate the calculated macroscopic average doses to the biologically and therapeutically effective cell doses taking into account the distribution of the tritium of TRA 119 among the different cells and within the cells, together with the appropriate time factors

As with all the previous therapeutic applications of the internal use of radioactive isotopes, this development is basically empirical but every effort must be made to establish some form of quantitative dosimetry

**Discussion**

Measurements of the specific activity of specimens of tumour and some other tissues are given in Table 2 for the 6 selected cases Table 3 gives the measurements of the specific activity in one of these, Case 71, after intra arterial injection of 10 8 curies of TRA 119

In Table 2 the specimens of tumour from parts of which autoradiographs are presented are indicated by asterisks Representative autoradiographs for these specimens are shown in Figs 1 to 7 It is to be noted that the grains are in focus so that the cells are in general out of focus For Case 49 the histologic appearance of part of the biopsy specimen is shown in Fig 2a at low magnification to demonstrate the small proportion of the volume of the metastatic tumour mass occupied by tumour cells In studies of the autoradiographs of these and other cases approximate estimates have been made of the proportion of tumour and stroma cells labelled and the mean grain count per labelled cell

The first problem to be discussed is the assessment of the value of the D A R which is relevant to the production of therapeutic effects and to the estimation of the dose of radiation delivered The calculated values of the macroscopic D A R for the different tumours are of particular interest and must be considered in relation to the mode of administration of the TRA 119 — whether intravenous or intra arterial — the proportion of the macroscopic specimen of tumour occupied by tumour cells as shown by histology and the distribution of the radioactive material both in the tumour and normal cells and within the tumour cells as shown by autoradiography

For Case 66 of recurrent adenocarcinoma of the caecum the macroscopi D A R for the biopsy specimen taken at 30 min after intravenous injection o 9 9 curies of TRA 119, had the value 1 64 which must be regarded as signifi cantly greater than unity The histologic structure, as seen in the autoradio



Fig 2 Same case as in fig 1 Section of biopsy specimen (upper) × 6 1 Autoradiograph of autopsy specimen (lower) × 1 000

graphs in Fig 4 shows that there is only a very little stroma but that the specimen contains considerable acinar and intercellular spaces, in addition to the tumour cells Measurements showed that about two thirds of the area of the sections was occupied by cells and about 60 % by tumour cells Accordingly, it can be assumed that about 46 %, say 50 %, of the volume of this specimen was occupied by tumour cells The autoradiographs show that almost all the tumour cells were labelled under the experimental conditions Crude values for the mean grain counts per cell were about 16 for tumour cells and about 6 for stroma cells with wide variation among cells It seems reasonable to conclude that the D A R for tumour cells i e, in relation to the mean concentration of radioactivity average over the whole body had a value of about 3 3 This value will be considered again later in relation to the concentration of tritium within the tumour cells and the problem of cell dose However,

it is of interest that in this case, the value of the D A R for the tumour cells is greater than unity after intravenous injection of TRA 119

For Case 49 of recurrent adenocarcinoma of the rectum the macroscopic D A R for the biopsy specimen from the metastases in the anterior abdominal wall at 30 min after intravenous injection of 1 4 curies of TRA 119 had the value of 1 04, which is not significantly different from unity However it is important to note that histology showed a very substantial proportion of the specimen to be occupied by fibrous stroma (Fig 2) Measurements showed that only 7 6 % of the area of a section of the biopsy specimen was occupied by tumour including acinar spaces The histologic structure (Fig 2) suggests infiltration by the well differentiated adeno carcinoma in association with an extremely marked stroma reaction Accordingly in this case spherical symmetry is not likely and it is best to assume that only about 8 % of the volume of the biopsy specimen was occupied by tumour including acinar spaces The autoradiographs (Fig 1) show a high degree of selective uptake of tritium in many of the tumour cells and apparently all the tumour cells at the growing point of the acinus shown, however there is only a low uptake in the stroma, both for the cells and for the matrix Quantitatively the grain count per arbitrary unit area of section was approximately 1 09 for the tumour cells and approximately 0 047 for the stroma, the very low background count was neglected About 65 % of the total radioactivity in the macroscopic specimen was concentrated in the tumour which occupied only about 8 % of the total volume so that the microscopic D A R for the tumour cells had a value of not less than about 8

The autoradiographs of sections of specimens of the same metastases obtained at autopsy in Case 49 are shown in Fig 2b Even at 135 days after the last intravenous injection of 2 64 curies of TRA 119, some tritium still persisted in a few areas in degenerating remains of tumour cells there was no labelling of the stroma cells No labelling was seen in actively proliferating tumour cells These findings suggest that there is a long biologic half life of the incorporated tritium for some of the tumour cells and that delayed degeneration of tumour cells is possible under some circumstances as a late result of the uptake of TRA 119 This matter needs further investigation

For Case 80 of recurrent carcinoma mammae the macroscopic D A R for the biopsy specimen of a metastatic nodule in skin taken at 35 min after intravenous injection of 10 1 curies of TRA 119 had the value 1 03 which is, of course not significantly different from unity The histologic examination and the autoradiograph (Fig 6) showed the specimen to be largely occupied by tumour cells with relatively little stroma and few stroma cells The autoradiograph shows the presence of tritium in most of the tumour cells but grain counts showed that about one third of the tumour cells had 2 grains or less per cell while the approximate mean grain count for the rest of the tumour cells was about 6 grains per cell with wide variation between cells Almost all the

stroma cells seen contained either no grains or one grain per cell under the present experimental conditions Accordingly there is no convincing evidence for a useful concentration of tritium in the tumour cells or for a value of the microscopic D A R for the tumour cells substantially greater than unity in Case 80

At this point mention may be made of two cases, in which apparently satisfactory autoradiographs of biopsy specimens showed no appreciable labelling of the neoplastic cells after intravenous injection of TRA 119 For one of these Case 63 of advanced recurrent carcinoma mammae which had arisen during lactation, the specific activity of the preparations of TRA 119 used was low, viz 40 and 42 curies per mM, however the failure of uptake may be attributable to the nature of the tumour since there was evidence of uptake into HeLa cells in tissue culture In the other case, Case 72 of advanced mycosis fungoides after much external irradiation the specific activity of the preparation of TRA 119 used was 62 curies per mM but this preparation was found to show negligible uptake into the HeLa cells on testing in tissue culture Accordingly, at present it is not possible to draw any conclusions about the uptake of TRA 119 into the neoplastic cells in mycosis fungoides

The evidence concerning the values of the D A R for the tumour in cases treated by intra arterial administration of TRA 119 is of particular interest in relation to the possibility of treating patients with relatively localised but otherwise untreatable malignant disease

A number of problems are raised by Case 52, of recurrent nodules of malignant melanoma, treated by means of three intra arterial injections of TRA 119 The biopsy of a nodule of tumour taken at 30 min after the first intra arterial injection of 1 5 curies of a preparation of TRA 119 of specific activity 87 curies per mM had a value of the macroscopic D A R of 2 72 The biopsy of adjacent muscle had a D A R of unity and peripheral blood 2 6 For the biopsy of another nodule of tumour taken at 41 min after the third intra arterial injection of 9 8 curies of a preparation of TRA 119 of specific activity 56 curies per mM, the macroscopic D A R was only 0 47 The histologic and autoradiographic appearances of this specimen are characterised by patchy uptake of tritium, with many areas with little demonstrable uptake, but some areas such as those shown in Fig 3, with considerable uptake into apparently all the tumour cells and little or no uptake into stroma cells However, in some of the areas of considerable uptake into tumour cells, there is a rather high local background Only a few of the tumour cells are pigmented The histologic appearance of patchy uptake in the biopsy specimen after the third injection probably reflects a changing non uniformity of the blood supply in these secondary nodules at different times It is possible that the relatively low uptake expressed in terms of $\mu$C per gram of wet tissue per curie injected may be associated with a poor batch of TRA 119 of rather low specific activity, further, the two previous injections may have produced radiation effects In any case, it is of

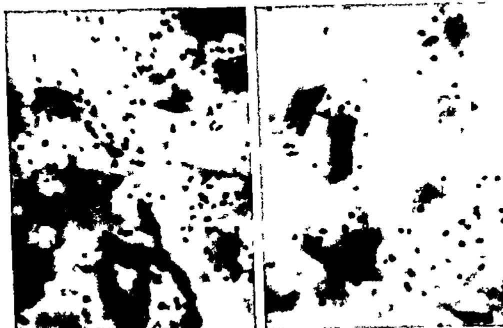


Fig 3 Case 59 Autoradiographs of section of metastatic nodule of malignant melanoma × 1 900

great interest that in this patient there appeared to be late retrogression of the secondary nodules including retrogression of new nodules which had developed since the injections This observation does not refer to two nodules which appeared to be growing and were treated with single doses of 1 750 r of roentgen rays delivered to localised small fields of diameters 1 5 and 2 0 cm respectively Although the late retrogression of the secondary nodules observed at 135 days after the last injection may be attributable to the treatment, it is difficult to be certain of this, because 'the behaviour of no other tumour is so unpredictable as that of melanoma and occasionally a melanoma [illegible] has already metastasized undergoes spontaneous retrogression (see WILLIS [illegible] p 908)

The highest values of the specific activity of biopsy specimens of tumour [illegible] of the corresponding macroscopic D A R so far attained have been [illegible] in Case 71, of extensive recurrent squamous carcinoma of the [illegible] ear The patient was treated, after failure of surgery and radiotherapy [illegible] arterial injection of 10 8 curies of TRA 119 (of specific activity 69 [illegible] per mM) through a catheter into the external carotid artery which [illegible] been exposed surgically The arteriogram showed partial thrombosis of [illegible] carotid artery but filling of the occipital branch, with increase in [illegible] and patchy blood supply to the region of the tumour after intra arterial [illegible] of

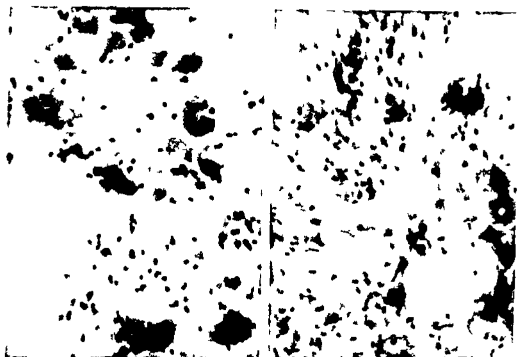


Fig 4 Case 6 Autoradiographs of section of metastasis of adenocarcinoma of caecum 1 900

tolazoline (Priscol), which was used as a vasodilator before the injection of TRA 119 It must be concluded that in this case the blood flow through most of the tumour was unusually slow The patient s general condition was poor Unfortunately at about 3 days after the intra arterial injection he became confused, he then deteriorated and died with severe bronchopneumonia at 14 days after the injection At autopsy, the histologic examination of the edge of the ulcer showed severe degenerative changes in the carcinoma cells these changes are consistent with irradiation by the TRA 119 at a therapeutic level

The value of the macroscopic D A R for a biopsy taken from the anterior part of the tumour at 30 min after the intra arterial injection of 10 8 curies of TRA 119 was 39 For further biopsies taken at 3 1/2 hours after the intra arterial injection, the D A R for a specimen from the anterior part of the tumour was only 1 64, while the D A R for a specimen from the posterior part of the tumour was 7 9 The autoradiographs for this latter specimen are shown in Fig 5 There is considerable variation in the histologic appearances especially with respect to differentiation of the squamous carcinoma cells, in different parts of the sections of this specimen However, throughout the specimen there is heavy labelling of tumour cells and only slight labelling of stroma cells Under the experimental conditions, the value of the mean grain count was about 35 per cell for the tumour cells and about 5 per cell for adjacent stroma cells



Fig 5 Case 71 Autoradiographs of section of recurrent squamous carcinoma of pinna × 1 900

with wide variation among cells in both cases The specimen consisted largely of tumour cells with relatively little stroma Accordingly for the biopsy specimen in question, the effective microscopic D A R for the tumour cells had the value of at least 8 It is to be noted however that there were areas of tumour with very much lower uptake

The specific activity of the autopsy specimens in this case are given in Table 3 The findings are similar to those with TRA 72 (MARRIAN MARSHALL and MITCHELL 1961 MITCHELL 1961) The ratio of the specific activity of a specimen of tumour to that of red bone marrow is 4 0 Again it was noted that the macroscopic appearances of the tumour were very variable in different parts with great differences in the vascularity The specific activity of the specimen of kidney was about the same as that of tumour The values for the small intestine and testis were about half those for tumour and kidney and about twice that for bone marrow The value for liver was not high being somewhat less than that for the small intestine It is of interest that the values for specimens of brain are about the same as that for bone marrow The detailed interpretation of these results is difficult The tissues remaining for examination at autopsy are likely a priori to include a selection of cells which both are relatively radio-

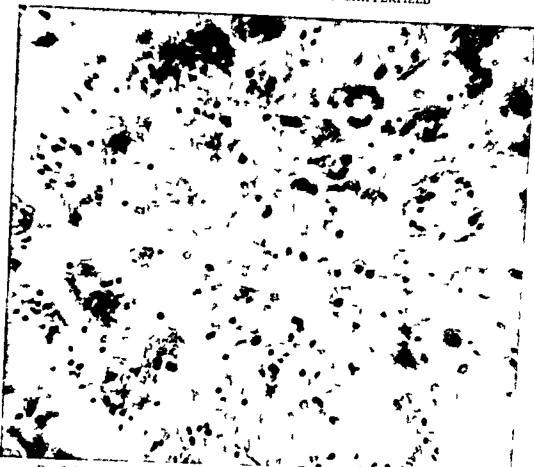


Fig 6 Case 89 Autoradiograph of section of metastasis of carcinoma mammae × 900

resistant and have shown a relatively low uptake of drug The specimen of tumour showed severe degenerative changes almost certainly due to irradiation

For Case 86 of recurrent adenocarcinoma of the rectum the value of the macroscopic D A R for the biopsy specimen of tumour taken at 30 min after intra arterial injection of 9 7 curies of TRA 119 was only 1 58 Histology showed rather widely separated tumour cells with some acinar spaces and very little stroma The autoradiographs (Fig 7) show labelling of apparently all the tumour cells but with wide variation from dense labelling of many tumour cells to only slight labelling of others especially in some areas where probably the blood supply was poor

Evidence concerning the distribution of the TRA 119 within the cells can be deduced from the autoradiographs The limiting factor is the resolution, with which is associated the image spread It is to be noted that the sections

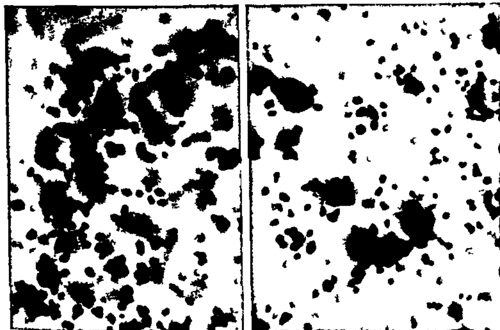


Fig 7 Case 86 Autoradiographs of section of metastasis of adenocarcinoma of rectum × 1 900

of the cells are of thickness about 5 μ so that in relation to the range of the beta particles of tritium, the sections approximate closely to layers of infinite thickness At a distance of 5 μ of unit density tissue from a point source of tritium the dose rate has fallen by a factor of about 5 × 10 [6] (ROBERTSON and HUGHES 1959) The tumour cells show great variation in size Representative mean values of the diameters are 4 2 μ for the nucleus and 6 5 μ for the cell (cf Case 66) and 8 μ for the nucleus and 11 μ for cell (cf Case 49) Under the experimental conditions the apparent grain size ranges from about 0 4 μ to about 1 0 μ Tracks and parts of tracks are viewed at angles ranging over 2 π

It is concluded that in most tumour cells the compound TRA 119 is present in the cytoplasm probably with concentration immediately outside and perhaps within the substance of the nuclear membrane, in some of these cells there is concentration in the regions of the nucleoli sometime to a high degree Apart from the nucleoli there appears to be little or no compound in most of the nuclei Probably there is a high concentration in some cells in metaphase and anaphase chromosomes but this subject needs further investigation There is almost certainly a higher concentration of compound in proliferating tumour cells than in the cells in non proliferating parts of the tumour In most cases there appears to be negligible uptake in degenerating tumour cells These findings are consistent with earlier studies of the distribution of Synkavit using flu

orescence microscopy (MITCHELL 1955) and also with the inhibition of part of RNA synthesis by Synkavit (MARRIAN 1959).

The next part of the problem is the evaluation of the effective cell dose. The simplest model is to assume that the distribution of the compound, TRA 119, is uniform within the cytoplasm and nuclear membrane and that the cell and the nucleus are spherical. For a cell of diameter 11 $\mu$ with nucleus of diameter 8 $\mu$, the D.A.R. for the cytoplasm is increased in relation to that calculated for uniform distribution throughout the whole volume of the cell by a factor of 1.63; for a cell of diameter 6.5 $\mu$ with nucleus of diameter 4.2 $\mu$, the D.A.R. for the cytoplasm is increased by 1.37. These are not large factors. Moreover, it is likely that only the compound present in and immediately outside the nuclear membrane, meaning within a shell outside the nuclear membrane of thickness about 1/2 $\mu$, make an appreciable contribution to the dose delivered by the tritium to the nucleus and its contents. It is to be noted that at 0.5 $\mu$ from a point source of tritium, the dose rate has fallen to about 8 % (ROBERTSON and HUGHES 1959). It is difficult to estimate the effects of irradiation by tritium in the regions of the nucleoli. However, the high degree of radiosensitivity of the nucleoli, as shown in microbeam studies (SEED 1960), must be noted. Even if it is assumed that half the tritium in the cell is concentrated in a spherical shell of thickness 0.5 $\mu$ surrounding the nuclear membrane, the dose of radiation delivered within the nucleus near the inner surface of the nuclear membrane is such that it is not likely that the effective value of the D.A.R. is raised above the average cell value by a factor of more than about 1.5, or less for small cells. It seems reasonably certain that a substantial proportion of the nuclear contents receive only a small or negligible dose of radiation.

These considerations suggest that until much more precise information is available, the best approximation to make is to assume that the relevant values of the specific activity and the D.A.R. correspond to the macroscopic values averaged over tumour cells. This procedure may in some cases underestimate the mean value of the dose averaged over all tumour cells. This use of the mean value is open to the objection that viable tumour cells with uptake much less than the average value may receive inadequate doses of radiation. To some extent, this factor can be assessed by autoradiography in terms of the distribution of grain counts per cell. It may be offset to a certain extent by the persistence of tritium in the tumour cells irradiated at lower dose rate. Nevertheless, this problem of low dosage in some of the tumour cells is important and may prove to be the factor limiting the possibility of cure by means of a radioactive drug.

Within the limitations discussed, it is now possible to consider the approximate estimate of the mean dose of radiation received by the tumour cells in the selected cases.

For Case 66, of recurrent adenocarcinoma of the caecum, the relevant mean specific activity of the tumour cells had the value of about 600 $\mu$C per gram

This corresponds to an initial dose rate of about 176 rad per 24 hrs which is equivalent biologically, assuming the value of 1 7 for the P B E , to about 300 r of $^{60}$Co gamma radiation per 24 hours However, the B H L of the tritium in the tumour in this case was only about 1 4 days so that it was only possible to deliver a total dose of about 600 r corresponding to the mean life of about 2 days This conclusion is in agreement with the clinical observation that no improvement followed the intravenous injection of 9 9 curies of TRA 119 The possibility of repeated intravenous injections must be raised in retrospect although it is unlikely that a therapeutically useful dose of radiation could have been delivered in this case

For Case 49 of recurrent adenocarcinoma of the rectum, it has been shown that the D A R for the tumour cells had a value of not less than 8 Accordingly the relevant specific activity of the tumour cells is about 226 $\mu$C following the intravenous injection of 1 4 curies of TRA 119 using a preparation containing about 8 mg of compound The initial effective dose rate is thus at least about 112 r per 24 hours With a long B H L not inconsistent with a value of 13 days or even longer as suggested by the findings in autopsy specimens, it is not unreasonable to expect some palliative effect of the radiation delivered Moreover it is likely that by intravenous injection of 8 curies of TRA 119 corresponding to the amount of 11 curies per 70 kg of body weight which is now considered justifiable, an initial dose rate corresponding to about 640 r per 24 hours would have been attained in the tumour cells

For Case 80 of recurrent carcinoma mammae, the value of the specific activity of the tumour cells must be taken as 103 $\mu$C per gram, although it is realised that this may be an underestimate The equivalent initial dose rate is thus at least 53 r per 24 hours Even assuming a long B H I for the tritium in the tumour cells, it seems doubtful whether the observed relief of pain could be attributed to irradiation at this dose level The amount of 10 1 curies of TRA 119 injected intravenously was contained in 74 mg of the chemical compound ordinary Synkavit even in larger amounts does not relieve pain in these cases The question of a psychologic effect must be raised but the possibilities of radiosensitization and of underestimation of the cell dose must be considered

The selected cases treated by intra arterial injection raise many problems For Case 52 of recurrent nodules of malignant melanoma it must be emphasised that there is no evidence of the delivery of equivalent dose rates of radiation of more than about 40 r per 24 hours from each of the three intra arterial injections However in view of the observed late retrogression of the secondary nodules the possibility of a very long B H L of the tritium in the tumour cells must be considered but the question of spontaneous retrogression must be raised

For Case 71 of extensive recurrent squamous carcinoma of the pinna of the ear the high values of the specific activity in the tumour cells are consistent with the delivery of doses of radiation at the therapeutic level The remarkably

high value of 8 990 µC per gram found for the 30 min biopsy from the anterior part of the lesion is probably only a short lived concentration With the poor circulation through the tumour observed in this case, the values of the specific activity for the biopsy specimens at 3 1/2 hrs after the intra arterial injection of 10 8 curies of TRA 119 are likely to give more reliable estimates of the doses of radiation delivered For the biopsy from the anterior part of the lesion, the specific activity of 378 µC per gram corresponds to an effective dose rate of 188 r per 24 hrs, for the biopsy from the posterior part of the lesion, the specific activity of 1 815 µC per gram corresponds to a dose rate of 904 r per 24 hrs The specific activity of the autopsy specimen is not inconsistent with a value of the B H L of about 4 4 days Accordingly, on the basis of a value of about 6 3 days for the mean life of the tritium in the tumour, the total doses delivered would be about 1 200 r for the anterior part of the lesion and about 5 700 r for the posterior part It is to be noted that the anterior part of the lesion with the very poor blood supply was in the area previously treated by external radiotherapy The results for the biopsy specimen from the unirradiated posterior part of the lesion suggest that it may be possible to deliver a curative dose of radiation to a squamous carcinoma by means of intra arterial TRA 119

The results for Case 86, of recurrent adenocarcinoma of the rectum, are disappointing, perhaps because of the poor blood supply to the recurrent mass in the ischiorectal fossa and perineum, but possibly because the tumour bed area was washed through with 50 ml of saline immediately before the intra arterial injection of, first Priscol, and then the TRA 119 The equivalent dose rate delivered was about 114 r per 24 hours, which could be expected to produce some palliative effects if associated with a long B H L of the tritium in the tumour cells Temporary relief of pain was in fact observed

## General discussion and Conclusions

The results provide evidence for some degree of selective concentration of TRA 119 in the tumour cells in relation to normal cells in some cases of certain types of malignant disease The estimated doses of radiation delivered by the tritium are consistent with the clinical finding that after intravenous injection of TRA 119, palliative effects may be produced in cases of highly radiosensitive conditions such as testicular seminoma and Hodgkin s disease, and also in certain cases of slowly progressive recurrent adenocarcinoma of the gastro intestinal tract

Intra arterial administration of TRA 119 appears to be necessary to attain therapeutic levels of the dose of radiation in the attempted treatment of patients with relatively localised but otherwise untreatable malignant disease of the histologic types of squamous carcinoma, melanoma and adenocarcinoma The

present evidence together with that of earlier studies with TRA 72, suggests the desirability of further investigation of the possible value of intra arterial therapy with TRA 119 in selected otherwise untreatable cases of squamous carcinoma of the head and neck, and also of the parametrium in carcinoma of the uterine cervix, stage III, malignant tumours of the limbs including melanoma and tumours of bone, and adenocarcinoma of the gastrointestinal tract

It is clear that much further investigation of the dose and time factors is required, particularly in connection with the need for repetition of intra arterial injections at intervals comparable with the biologic mean life of the tritium in the tumour In order to slow down the rate of blood flow through the tumour the suggestion has been made by our colleague Dr Aileen K Adams, that the intra arterial injection should be given under hypothermia

From a biochemical point of view, the selective uptake of TRA 119 into certain malignant cells is of interest particularly in relation to the recent findings of low concentrations of co enzyme Q in some tumours, and of the greater increase in the activity of certain oxidative enzymes produced by addition of co enzyme $Q_{10}$ or menadione in tumour than in homologous normal tissue (WATTENBERG 1961 OSTERBERG and WATTENBERG 1961)


## Acknowledgements

We wish to acknowledge with grateful thanks the most helpful and active collaboration of the staff of the Radiochemical Centre Amersham and especially its Director Dr W P Grove and of Roche Products Welwyn Garden City and especially Drs A L Morrison and K J Andrews

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## SUMMARY

An account is given of laboratory and clinical investigations of the therapeutic possibilities of a radioactive drug containing tritium in very high specific activity 2 methyl 5 6 7 tritritio-1 4 naphthaquinol bis (disodium phosphate) (TRA 119) Measurements of the specific activity of biopsy and autopsy specimens and autoradiographic studies are discussed in selected cases with special reference to dosimetry The results provide evidence for some degree of selective concentration of TRA 119 in tumour cells in relation to normal cells in some cases of certain types of malignant disease

## ZUSAMMENFASSUNG

Laboratoriums und klinische Untersuchungen über die therapeutische Wirksamkeit eines radioaktiven Heilmittels das stark aktives Tritium 2 Methyl 5 6 7 Tritritio-1 4 N phtha quinol bis (dinatriumphosphat) (TRA 119) enthalt werden beschrieben Messungen der spezifischen Aktivitat nach Probeexcision auf dem Sektionstich und autoradiographische Untersuchungen in ausgewahlten Fallen werden geschildert mit besonderer Rucksicht auf die Dosimetrie Die Resultate bestatigen die selektive Konzentration des TRA 119 in den Tumor zellen von gewissen Arten von malignen Geschwulsten

## RÉSUMÉ

Présentation d études expérimentales et cliniques sur les possibilités thérapeutiques d une substance radioactive contenant du tritium de très haute activité spécifique le 2 méthyl 5 6 7 tritritio-1 4 naphthaquinol bis (phosphate disodique) (TRA 119) Les auteurs examinent, en particulier au point de vue de la dosimétrie sur des cas sélectionnés les mesures de l activité spécifique de pièces biopsiques et autopsiques et les études autoradiographiques. Les résultats donnent la preuve d une certaine concentration sélective du TRA 119 dans les cellules tumorales par rapport aux cellules normales dans certains cas de certains types d affection maligne

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF S R KJELLBERG), SAHLGRENSKA SJUKHUSET GOTHENBURG SWEDEN

# GONAD DOSIMETRY IN DIAGNOSTIC RADIOLOGY WITH THE HIGH KILOVOLTAGE TECHNIQUE

by

HERMANN BOSCHE and SVEN ROLAND KJELLBERG

Radiography at kilovoltages of 150 or higher may in many circumstances possess certain advantages Reductions in the exposure time and the subsequent radiation dose are obtained and by the use of a small tube focus better image definition may be obtained

The main objection to the so called high kilovoltage technique would appear to be the cost involved in changing from a conventional radiographic technique but the only valid argument against the high kilovoltage technique advanced by various investigators would appear to be that the gonad dose increases 3 to 5 times when the kilovoltage rises

As previous results obtained in our department did not confirm this assertion the results of a new and extensive investigation are now presented

The following preliminaries to the tests took place

1 Checking of the roentgen equipment and of the exposure factors (kV mA sec) Negligible mA deviations will be considered in this report Cable capacity = [illegible]0 picofarads per meter

2 Checking of instruments (a) Philips electrometer type 37471/00 with measuring chamber 0-30-300 r/min type 37480/10 HVL 0 03—4 mm Cu for the test measurements and with chamber 1 3-10 r/min type 37488/10 HVL 0 07—2 mm Cu for SD/ED/FD measurements (b) EIL electrometer (Electronic Instruments Ltd) model 378 with standardized round graphite flat chamber 5 × 13 cm Chamber constant at 22 and 760 mm Hg = 1 05 for mr values The variation of the chamber for the various voltages was less than 3

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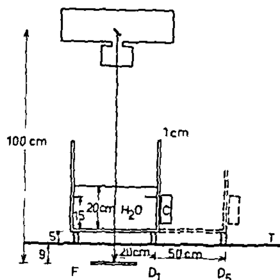



Fig 1 Experimental model

3 Checking of the densitometer EEL Universal for constant sensitivity extended over a few days

The abbreviations used are as follows
SD = superficial dose
FD = film dose (in film plane)
sF = small field 10 × 10 cm collimated at the phantom base
lF = large field 15 × 15 cm collimated at the phantom base
CCD = chamber-central beam-distance
S = film blackening
ED = exit dose
GD = gonad dose

*Testing arrangements (see Fig 1)*

1 Siemens diagnostic tube 200 kV, 30/50 kW large focus of 1 mm with a filter of 0 2 mm Fe was used 5664 exposures had been made with this tube at the beginning of the investigation

2 Elema Schönander Triplex Optimatic three phase generator 150 cycles with additional transformer Minimum switching time 1 53 msec (with due consideration to cable capacity)

3 Elema Schönander Coordinat Universal table with Elema grid 7 1

4 Gevaert Rapid film and Schmidthals cassettes with Siemens Rubin intensifying screens

5 *Elema Jarnh automatic film processing machine type Z*

6 Phantoms of 1 cm plexiglass 40 × 40 cm and 30 × 30 cm with 15 cm or 20 cm water depth

7 Distances Focus-film 100 cm focus-table 91 cm focus-phantom 86 cm focus water surface 71 or 66 cm

8 Field collimation at the phantom base with Siemens collimator

9 Measuring points the middle of the chamber in the central beam on the water surface = SD *the middle of the chamber in the central beam on the bottom of the phantom* = ED the middle of the chamber in the central beam on the film plane = FD chamber on the lateral wall at half water height at a distance of 20 to 50 cm from the central beam = GD

*Test series*

The test series were tabulated in proper sequence In the evaluation only the results of complete test series that had given constant values in repeated measurements after elimination *of initial sources of error were used Preliminary tests provided identical relationships* between values

All measurements were made under the same initial conditions In order to ensure constant radiographic data constant film blackening was required for the voltage steps from 60 to 190 kV

*Measurements*

1 Determination of radiographic data by adjusting the mA value and time factor (sec) to 60 80 110 140 190 kV One series with a film blackening of 0 6 and another one of *1 3* was obtained

2 Measurement of the superficial dose exit dose and film dose related to a film blackening of 0 6 and 1 3 with a small and a large field and in a 15 cm water phantom

**Table 1**

*Comparison of the film blackening with various intensifying screens*

| kV | mA | sec | Blackening of the film with Screen 1* | Screen 2 | Screen 3 |
|---|---|---|---|---|---|
| 60 | 200 | 1 0 | 0 77 | 0 65 | 1 10 |
| 80 | 200 | 0 2 | 0 80 | 0 65 | 1 10 |
| 120 | 200 | 0 02 | 0 74 | 0 60 | 0 9[illegible] |
| 150 | 200 | 0 007 | 0 72 | 0 55 | 0 [illegible] |
| 200 | 200 | 0 003 | 0 75 | 0 60 | 1 10 |

* This screen was used in the experiments

3 Checking and correction of exposure data because of excessive variation
4 Measurement of film dose related to a film blackening of 0 6 and 1 [illegible] large field and in 15 cm water with corrected values
5 As under (4) but in 20 cm water
6 Determination of new exposure data related to a film blackening of 0 7[illegible] mA was kept constantly at 200 and the exposure time (sec) was adjusted [illegible]
These data were used for the following tests Nos 7 to 14
7 Measurement of superficial dose exit dose film dose with 0 [illegible] filter a small and large field and 15 cm water (Tables 2 and 3)
8 Measurement as under (7) but with 20 cm water (Tables 4 and [illegible]

**Table 2**

*Relation SD ED FD in 15 cm water and field 10 × 10 cm with 0 2 mm [illegible]*

| Filter | Surface dose in mr Fe | Surface dose in mr Without | Exit dose in mr Fe | Exit dose in mr Without |
|---|---|---|---|---|
| 60 kV | 79 0 | 173 0 | 1 30 | 2 20 |
| 80 kV | 34 0 | 68 0 | 0 70 | 1 12 |
| 110 kV | 31 5 | 38 2 | 0 64 | 0 91 |
| 140 kV | 23 5 | 30 9 | 0 60 | 0 71 |
| 190 kV | 21 2 | 31 5 | 0 64 | 0 79 |

**Table 3**

*Relation SD ED FD in 15 cm water and field 15 × 15 cm with 0 [illegible]*

| Filter | Surface dose in mr Fe | Surface dose in mr Without | Exit dose in mr Fe | Exit dose in mr Without |
|---|---|---|---|---|
| 60 kV | 103 0 | 205 0 | 1 39 | 2 20 |
| 80 kV | 44 2 | 70 1 | 0 72 | 1 12 |
| 110 kV | 27 0 | 44 1 | 0 34 | 1 [illegible] |
| 140 kV | 23 4 | 33 0 | 0 32 | 1 2[illegible] |
| 190 kV | 22 5 | 32 7 | 0 36 | 1 [illegible] |

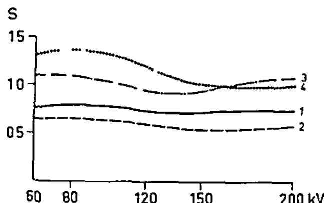



Fig 2 Relation of film blackening with different screens and same exposure data (screen 1 was used for the experiments)

9 Measurement of gonad dose with 0 2 mm Fe filtration and without filter small and large field 15 cm water with 20 35 and 50 cm chamber central beam distance

10 Measurement of gonadal dose as under (9) but with 20 cm water

11 Control measurement of film blackening and exposure factors For comparison 4 different screens were used screen combination 1 gave the most constant film blackening and was therefore used in the examinations (Table 1 Fig 2)

12 Exposure data unchanged repeat measurements of gonadal dose as under (9) Chamber central beam distance 20 25 30 35 and 50 cm (Tables 6 and 7 Figs 3 and 4)

13 Repetition of the measurements as under (10) distance as under (12) (Tables 8 and 9 Figs 5 and 6)

14 Control measurement of superficial dose curve in the range between 40 and 60 kV with and without filter

Exposure data were determined with an average film blackening of 0 74 for tube potentials of from 60 to 80 kV (Table 1)

A comparison of the blackening characteristics obtained with various intensifying screens confirm the radiographic data and the constant behaviour of the selected screen combination 1 with reference to film density (Table 4 Fig 2)

The values shown in Tables 2 and 3 indicate a steep drop in the superficial dose, especially between 60 and 120 kV The curve of the filtered radiation runs nearly parallel to that representing the unfiltered radiation

The values in Tables 4 and 5 have a relationship similar to those in Tables 2 and 3 In the case of 15 cm water and a small field, the exit dose is reduced to a fifth in the voltage range from 60 to 140 kV and in the case of 20 cm water and a large field the exit dose decreases to a fourth within the same voltage range A slight increase in the exit dose is observed in the voltage range from 140 to 190 kV in both tests and this increase corresponds to a small measurable lower vol

**Table 4**

*Relation SD FD FD in 20 cm water and field 10 × 10 cm with 0 2 mm iron filter and without filter*

| Filter | Surface dose in mr | | Exit dose in mr | | Film dose in mr | |
|---|---|---|---|---|---|---|
| | Fe | Without | Fe | Without | Fe | Without |
| 60 kV | 100 0 | 225 0 | 3 04 | 4 21 | 0 19 | 0 26 |
| 80 kV | 42 0 | 74 4 | 2 13 | 2 90 | 0 13 | 0 20 |
| 110 kV | 38 0 | 47 0 | 1 13 | 1 21 | 0 09 | 0 12 |
| 140 kV | 29 0 | 39 0 | 1 05 | 1 07 | 0 18 | 0 16 |
| 190 kV | 23 5 | 38 7 | 1 12 | 1 20 | 0 15 | 0 20 |

**Table 5**

*Relation SD ED FD in 20 cm water and field 15 × 15 cm with 0 2 mm iron filter and without filter*

| Filter | Surface dose in mr | | Exit dose in mr | | Film dose in mr | |
|---|---|---|---|---|---|---|
| | Fe | Without | Fe | Without | Fe | Without |
| 60 kV | 112 0 | 245 0 | 4 90 | 6 81 | 0 30 | 0 42 |
| 80 kV | 48 0 | 83 0 | 3 12 | 4 21 | 0 22 | 0 31 |
| 110 kV | 43 0 | 48 0 | 1 83 | 2 02 | 0 17 | 0 20 |
| 140 kV | 31 2 | 40.2 | 1 51 | 2 00 | 0 20 | 0 25 |
| 190 kV | 29 0 | 38 0 | 1 65 | 1 80 | 0 22 | 0 30 |

ume dose The 'sag of the curve for the film dose in the range from 60 to 120 kV is based on the decrease of the absorption factor of the grid/cassette combination and on the increased luminescence of the intensifying screens The increase within the voltage range up to 190 kV is obviously related to the harder radiation

With reference to a constant film density and the radiographic data in accordance with Table 1 it is evident from Fig 3 and Table 6 that the gonad dose decreases with the distance from the central ray in the various kV ranges, the lower the voltage the more marked will this decrease be The shape of the curves corresponding to a specific distance from the central ray reveals that with rising voltage the gonad dose drops considerably Its minimum value is obtained at voltages of from 110 to 140 kV the increase with voltages of up to 190 is only slight and does not exceed the dose level obtained at 100 kV

The measurement values in Fig 4 and Table 7 show that the larger field influences the absolute values but not their interrelation Here again the gonad dose is markedly higher at 60 and 80 kV than at voltages higher than 100 kV The bundle of curves is denser with a 20 cm water phantom corresponding to a thick patient although the shape of the curves compared with findings of the previous test is not altered Here again the minimum value of each curve falls in the voltage range from 110 to 140 kV and the slight rise with voltages

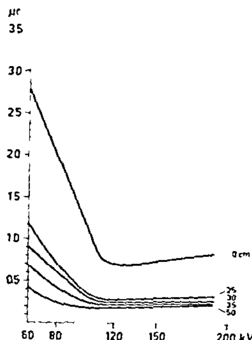



Fig 3 Gonad doses with 60 to 190 kV at different distances from field 15 cm water field 10 × 10 cm (see table 6)

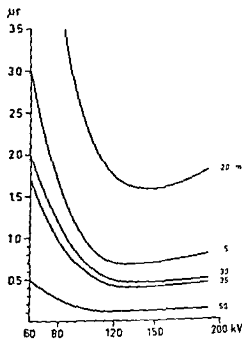



Fig 4 Gonad doses with 60 to 190 kV at different distances from field 15 cm water field 15 × 15 cm (see table 7)

up to 190 lies far below the values measured at voltages lower than 100 kV (Fig 5, Table 8) The gonad dose at 60 kV is 3 to 6 times greater according to the distance from the central ray than the one measured at 190 kV The increased scatter of the larger field results in a somewhat more marked rise in the gonad dose at 190 kV (Fig 6, Table 9), but it completely corresponds to the equally higher value obtained at 100 kV The gonad dose at 60 kV is still about 3 times higher at all distances measured than at 190 kV

## Results

The values given in Tables 2 3, 4 and 5 indicate the behaviour of the superficial dose, exit dose and film dose at voltages from 60 to 190 kV in relation to a constant film dose blackening

The steep drop in the superficial dose with increasing radiographic voltage has been confirmed by all research workers Because of the backscatter, which has also to be measured the dose on the phantom s surface is higher than when the measuring chamber is located in the same position but without a phantom This was previously shown by SCHAAL

**Table 6**

*Gonad doses in μ r in 15 cm water and field size 10 × 10 cm with 0 2 mm iron filter at different distances from field*

| | Chamber — central beam — distances | | | | |
|---|---|---|---|---|---|
| kV | 50 cm | 35 cm | 30 cm | 25 cm | 20 cm |
| 60 | 4 4 | 7 0 | 9 1 | 12 0 | 28 0 |
| 80 | 2 4 | 4 5 | 6 3 | 7 2 | 20 0 |
| 110 | 1 8 | 2 2 | 2 4 | 2 8 | 8 2 |
| 140 | 2 0 | 2 1 | 2 3 | 2 7 | 7 2 |
| 190 | 2 2 | 2 3 | 2 5 | 3 2 | 8 3 |

**Table 7**

*Gonad doses in 15 cm water and field size 15 × 15 cm with 0 2 mm iron filter at different distances from the field*

| | Chamber — Central beam — Distances | | | | |
|---|---|---|---|---|---|
| kV | 50 cm | 35 cm | 30 cm | 25 cm | 20 cm |
| 60 | 5 0 | 17 5 | 20 0 | 30 0 | 60 0 |
| 80 | 2 8 | 10 0 | 12 0 | 17 0 | 38 0 |
| 110 | 1 3 | 4 7 | 5 4 | 7 7 | 20 0 |
| 140 | 1 3 | 4 2 | 4 9 | 7 2 | 16 0 |
| 190 | 1 3 | 4 5 | 5 0 | 8 0 | 18 0 |

Doses in μ r

The exit dose follows by no means a linear course in relation to the constant film density required in practice The exit dose drops at 190 kV on an average by a third of the value obtained at 60 kV when various field sizes and object thicknesses are used The total volume dose is lessened owing to the more favourable relationship between superficial dose and exit dose in the case of rising voltages The film dose from its initial value obtained at 60 kV decreases up to 110 kV and rises again slightly with voltages up to 190 kV The fact that the curve does not follow a rectilinear course proves that the film density is a function of the kilovoltage There is a decrease in the film dose of 30 to 40 % when the potential is raised from 60 to 190 kV, depending on the object thickness and field size

The gonad dose curves (Figs 3 4 5 and 6) obtained by plotting the measured values (Tables 3 4 5, 6 7, 8 and 9) display a uniform course despite irregularities caused by measuring errors A high scatter dose is measured at 60 kV at distances of 20 25 30 35 and 50 cm from the central ray This dose has reached its half value at about 80 kV The lowest point of all curves for the various phantom thicknesses and field sizes is obtained between 140 and 110 kV this lowest value moves from 140 kV at a distance of 20 cm to

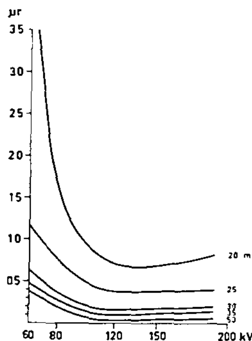



Fig 5 Gonad doses with 60 to 190 kV at different distances from field 20 cm water field 10 × 10 cm (see table 8)

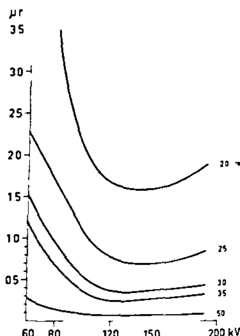



Fig 6 Gonad doses with 60 to 190 kV at different distances from field 20 cm water field 15 × 15 cm (see table 9)

110 kV at 50 cm When the radiographic voltages are pushed up to 190 kV, *the curves become slightly steeper, because under this condition the* effect of the increased harder scatter is felt This rise is however so small that the end of the curve at 190 kV does not exceed the value obtained at 100 kV The flat end of the curve represents only a moderate change in the gonad dose between 110 and 190 kV as compared with the steep rise at the beginning of the curve *Moreover, the curves give the impression that it is the field size* rather than the phantom thickness that affects the gonad dose

## Discussion

These measurements of the superficial dose and exit dose correspond with *the data obtained by other authors The values differ only in* their absolute magnitude The present writers used for all kV ranges tested added filtration of 0 2 mm Fe With regard to the resultant radiation homogeneity, this corresponds to 4 mm Al filtration but offers in compensation a gain in dose rate (1 2)

Grids, filters *intensifying screens and films* remained constant during the tests There is no doubt that a higher blackening and a modification of the grid filter, intensifying screen or film, change the measured values in their order of magnitude although the type of curves obtained will be maintained

**Table 8**

*Gonad doses in 20 cm water and field size 10×10 cm with 0.2 mm iron filter at different distances from the field*

| | Chamber — Central beam — Distances | | | | |
|---|---|---|---|---|---|
| kV | 50 cm | 35 cm | 30 cm | 25 cm | 20 cm |
| 60 | 3.8 | 4.9 | 6.5 | 12.0 | 43.0 |
| 80 | 2.1 | 2.8 | 3.8 | 7.8 | 17.0 |
| 110 | 0.35 | 1.4 | 1.9 | 4.2 | 8.0 |
| 140 | 0.4 | 1.3 | 1.9 | 3.8 | 7.0 |
| 190 | 0.5 | 1.4 | 2.0 | 4.1 | 8.0 |

Doses in $\mu$r

**Table 9**

*Gonad doses in 20 cm water and field size 15×15 cm with 0.2 mm iron filter at different distances from the field*

| | Chamber — central beam — distances | | | | |
|---|---|---|---|---|---|
| kV | 50 cm | 35 cm | 30 cm | 25 cm | 20 cm |
| 60 | 2.7 | 12.0 | 15.0 | 23.0 | 51.0 |
| 80 | 1.5 | 7.0 | 9.8 | 17.0 | 35.0 |
| 110 | 0.75 | 2.8 | 4.3 | 9.0 | 18.0 |
| 140 | 0.8 | 2.8 | 3.8 | 7.0 | 16.0 |
| 190 | 0.9 | 3.2 | 4.6 | 8.5 | 19.0 |

Doses in $\mu$r

The impression gained by the writers that the thickness of the patient has only a slight influence on the gonadal dose values in conjunction with HAYBITTLE's statement that the field size is not as decisive as the distance of the gonads from the field suggests that the characteristic shape of the curves obtained make them generally acceptable for roentgen diagnosis

Many papers dealing with the changes in the gonad dose with varying radiographic potential have appeared The results are by no means uniform and the reports that the gonad dose increases by as much as 3 to 5 times when the tube potential is raised into the high kV range is limited to few yet frequently quoted test results These papers almost without exception referred to a constant exit dose obtained in phantom measurements In contrast to this it emerges from Tables 2 3 4 and 5 that the exit dose is not suitable as a reference point if the present conditions are to be met OESER found in phantom measurements at tube potentials up to 100 kV that the gonad dose appreciably rises in the high kV ranges With reference to the exit dose MOHR arrived at the same results by phantom measurements at kilovoltages up to 200 kV Accounts by the same author on results obtained in patients during examinations made by

operators in various hospitals under different conditions are not conclusive as he indicated only mean values for potentials up to 150 kV. MICHAL & SVOBODA, while emphasizing the advantages of high kV technique for phantom measurements with a constant exit dose, also drew the conclusion that the gonad dose increases. SCHAAL however found that the increase in the gonad dose is less marked if the measurements are made behind the grid, a result which was confirmed by measurements effected by MOHR. CEX & FRIK in making measurements under the same conditions also observed that the gonad dose rises with a higher tube potential but argued that this increase might possibly be affected by the grid, intensifying screen and film factors. KLOTZ & SEELENTAG, in a thesis published in 1961, stated that during measurements made in a living subject the gonad dose increased with rising potential, but laid the emphasis of the investigation on the resultant dosages actually obtained in routine examinations. KLOTZ (1958) however, reported that the difference in the magnitude of the gonad dose with soft and hard radiation (50 to 200 kV) is not noticeable although he too referred to a constant exit dose. There appears to be a contradiction in the paper of MARTIN, who in a table for thorax radiography gave a reduction of the dose to the ovaries when the radiographic voltage and the filtration were raised. Mention is made in the pertinent text, however, of an increase in the gonad dose under the same conditions; detailed voltage and filtration data are not available in the clinical application of these investigations.

It emerges from a large number of publications (BURNEY, HAMMER JACOBSEN, HOLTHUSEN, OSBORN, WINDEYER, ZUPPINGER et coll.) that the gonad dose received in roentgen diagnosis is on an average very small, it is also lower than the dose received from the daily exposure to natural ambient radiation. Consequently a dose increase or decrease certainly lies within a magnitude that in itself can be tolerated. It must be stressed, however, that this knowledge does not free us from the obligation of keeping the individual dose of the patient as low as possible.

Although the results contained in the publications that have been quoted only in part are not uniform, they have nevertheless produced the impression that the higher gonad dose should restrict the use of high kilovoltages. The present results corroborate the fact, already presumed in some papers, that *the gonad dose does not rise when radiographic voltages in the high kV range are employed.* More than that, they demonstrate that at the distances used in daily practice, the gonad exposure is considerably higher at voltages from 60 to 100 kV than from 100 to 200 kV.

## Acknowledgements

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## SUMMARY

The superficial exit and scatter doses corresponding to the gonad dose were measured in a phantom at kilovoltages of from 60 to 190 kV with a tested installation and under given conditions Proof was obtained that the gonad dose decreases both at short and long distances when the tube potential is increased The gonad dose is considerably higher at radiographic voltages from 60 to 80 kV than in the 100 to 200 kV range



## ZUSAMMENFASSUNG

An einem Phantom wurden die Einfallsstrahlung die Ausfallsstrahlung sowie die Streuung bei Verabreichung einer Gonadendose bei Spannungen von 60 bis 190 kV mit einer geeichten Apparatur und unter kontrollierten Bedingungen gemessen Es wurde bestatigt dass die Gonadendose sowohl bei kurzen als auch bei langen Abstanden abnimmt wenn man die Rohrenspannung vergrossert Die Gonadendose ist betrachtlich höher im Bereich der diagnostischen Spannungen von 60 bis 80 kV als im Bereich der Hartstrahltechnik von 100 bis 200 kV



## RÉSUMÉ

La dose superficielle la dose de sortie et la dose de rayonnement diffusé correspondant à la dose gonade ont été mesurées sur un fantôme sous des tensions comprises entre 60 et 190 kV avec une installation testée et dans des conditions déterminées Cette expérimentation prouve que la dose gonade diminue aussi bien a courte qu à longue distance quand la tension du tube augmente La dose gonade est considérablement plus élevée à des voltages radiographiques compris entre 60 et 80 kV qu entre 100 et 200 kV


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FROM THE DEPARTMENT OF MEDICAL PHYSICS, AND THE DEPARTMENT OF GERM FREE RESEARCH KAROLINSKA INSTITUTET, STOCKHOLM SWEDEN

# MINERAL PATTERN OF URINARY CALCULI FROM GERM FREE RATS

by

J E GLAS and B GUSTAFSSON

A frequent occurrence of urinary calculi was detected in a recent investigation in germ free rats (GUSTAFSSON & NORMAN 1962) Profound alterations in the urinary composition were found to be associated with the presence of numerous bladder stones which were observed almost exclusively in males When the animals acquired the flora of conventional rats however the urinary excretion after a short period returned to normal Conventional rats maintained on exactly the same diet were entirely free of calculi indicating that some specific etiologic factor for stone deposition was present under germ free conditions The present report concerns the morphology structure and mineral composition of bladder stones collected from a small number of germ free rats

*Germ free method* Germ free rats were reared according to the modified technique of GUSTAFSSON (1948 1959) and maintained on the semisynthetic diet D7 sterilized by autoclaving for 20 min at 121 C According to the analysis of the diet by a commercial laboratory the dry weight basis consisted of protein 21 4 % calcium 1 02 % phosphorus 0 48 % giving a Ca P ratio

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of 2 13 The animals were killed after various periods of time and the bladder stones were collected and kept at — 17° C

*Roentgen analysis* One to five calculi from each animal were examined by the powder roentgen diffraction technique The stones were cut in two equal halves, one of which was ground into a fine powder Representative samples, containing all the components present in each calculus were thus assumed to be obtained Diffraction patterns from such specimens were recorded with a cylindric Debye Scherrer camera 114 6 mm in diameter Ni filtered Cu radiation from a roentgen tube, operated at 40 kV and 20 mA was used throughout the diffraction experiments The cut surface of the remaining halves of the stones was ground as smooth as possible and a slice was cut parallel to the ground surface the ground sections obtained in this way had a thickness between 200 and 300 microns and were obtained from calculi from the majority of the rats In most cases regions having a different micro scopic appearance were noted in the cut sections and small pieces of such regions were dissected out for identification, a flat film microroentgen diffraction camera being used for this purpose Contact microradiograms of the sections were made prior to the dissection procedure on Kodak Maximum Resolution plates using Ni filtered Cu radiation as above These provided detailed information, due to the varying roentgen absorption characteristics, on the local distribution of the different chemical components building up the calculi

The crystalline salts present within the calculi were identified after comparing diffraction patterns from substances of known composition with those actually obtained from the stones Identification of one of the components (calcium citrate hexahydrate) was somewhat complicated by the lack of reference material as well as of recorded roentgen data for the particular hydrate present Several different preparations of different hydrated forms of calcium citrate were therefore produced, diffraction patterns from such precipitates (dried at room temperature for 48 hours) were recorded and compared with those obtained from the calculi

## Results and Discussion

Bladder stones from germ free animals appeared as well formed ovoid to spherical bodies varying in size from less than 0 5 mm to 7 mm The number and approximate size distribution of stones collected from five rats of different ages are given in the Table The external appearances and internal structure of calculi from each animal were identical, as revealed by microscopic examination of intact or fractured/sliced stones in reflected light Calculi collected from a single animal also showed uniform chemical characteristics

Three different chemical compounds were identified in the calculus material examined calcium citrate hexahydrate ($Ca_3(C_6H_5O_7)_2$ 6 $H_2O$), calcium

**Table**

*Numbers and size distribution of stones collected from five rats of different ages*

| Animal No | Age at sacrifice (days) | Number and size of calculi | Number of calculi examined | Components found in the calculi |
|---|---|---|---|---|
| 1 | 128 | 2 2 to 3 mm | 1 | Calcium oxalate dihydrate |
| 2 | 104 | 8 to 10 0 5 to 4 mm | 5 | Calcium citrate hexahydrate + calcium oxalate dihydrate |
| 3 | 208 | 8 to 10 0 5 to 3 mm | 4 | Calcium citrate hexahydrate + calcium oxalate dihydrate |
| 4 | 974 | 20 to 25 2 to 7 mm | 4 | Calcium citrate hexahydrate + calcium oxalate dihydrate + basic calcium phosphate (apatite) |
| 5 | 110 | *0 5 to 4 mm | 2 | Calcium citrate hexahydrate + calcium oxalate dihydrate |

*Cluster of ovoid stones connected by masses of calculus material

oxalate dihydrate ($CaC_2O_4$, 2 $H_2O$) and basic calcium phosphate, 'apatite ($Ca_{10}(PO_4)_6(OH)_2$) (see Table) The presence of the hexahydrate modification of calcium citrate within the stones was strongly suggested by the observation that a change in crystal structure from that of the tetrahydrate form was induced after the calculus citrate had been heated to 60 C for two hours The predicted temperature for the hexahydrate tetrahydrate transformation is 52 C, as shown by CHATTERJEE & DHAR (1924) Moreover diffraction patterns obtained from calcium citrate precipitates dried at room temperature and containing 6 1 moles of water were found to be identical with those recorded from the calculus citrate thus proving the existence of the hexahydrate modification in the stones Citrate occurred as the dominating component in the calculi and appeared as a white soft and rather loosely packed powder which easily decomposed into thin, curved lamellae when fractured Calcium citrate was occasionally found in the pure state in small volumes although it usually occurred admixed with calcium oxalate and sometimes apatite

Only in one case were stones found to be composed of pure calcium oxalate Calculi from animal 1 thus appeared as a cluster of closely connected brownish crystals arranged radially and having an individual size of about 100 to 400 microns

In calculi from other animals calcium citrate always formed a central core in combination with varying quantities of calcium oxalate The oxalate fraction mixed with the citrate, however, was always small and showed up in the microdiffraction patterns as spotty rings indicating a greater crystal size than the citrate

As judged from microradiograms and microroentgen diffraction tests there was an increasing proportion of oxalate towards the outer parts of the stones in most cases Calculi from animals 2 3 and 4 were all enveloped with a thin

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analysis involving the use of column and gas chromatography for the separation and identification of calcium oxalate and calcium citrate (GUSTAFSSON & NORMAN 1962)

The application of roentgen methods has yielded further information about the distribution of the various mineral components building up the calculi, and the crystalline nature of the different calcium salts present has been fully established It has also been possible to prove the existence of basic calcium phosphate in small quantities in stones from one animal

Data collected on the chemical composition of the calculi correlate well with the observed urinary excretion pattern of the rats Determinations of the electrolytes in the urine from a small group of rats thus showed the presence of high levels of calcium and citrate (5 to 10 times the values for the conventional rats) whereas the phosphorus content was low The occurrence of calcium citrate in the calculi is remarkable in view of its high solubility (2 1 grams per 1 000 ml water at 30 C) (CHATTERJEE & DAHR 1924) compared to that of other calcium salts present in the calculi (calcium oxalate and apatite)

The urinary concentrations of calcium and citrate ions during germ free conditions are however evidently high enough to keep the salt in its solid state The organization of the stones is in agreement with the finding that calculi disappeared during the ex germ free period and that the innermost part was then the first to dissolve (GUSTAFSSON & NORMAN 1962)

## SUMMARY

Bladder stones from germ free rats were investigated by means of microradiography and roentgen diffraction The calculi were found to be composed of three different calcium salts calcium citrate hexahydrate calcium oxalate dihydrate and basic calcium phosphate The proportions of these compounds and their local distribution within the stones were determined

## ZUSAMMENFASSUNG

Blasensteine von infektionsfreien Ratten wurden mit Hilfe von Mikroradiographie und Röntgendiffraktion untersucht Es wurde gefunden dass die Steine aus drei Kalksalzen zusammengesetzt waren Calciumcitrat hexahydrat Calciumoxalat-dihydrat und Calcium phosphat Der proportionale Anteil jedes Salzes sowie deren Verteilung innerhalb des Steines werden angegeben

## RÉSUMÉ

Les auteurs ont étudié en microradiographie et en diffraction de rayons roentgen des calculs vésicaux provenant de rats exempts de germes Ils ont constaté que ces calculs sont composés de trois sels de calcium différents le citrate de calcium hexahydrate l oxalate de calcium dihydrate et le phosphate basique de calcium Ils ont déterminé les proportions de ces composés et la localisation de leur répartition dans les calculs

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FROM STRAHLENTHERAPEUTISCHEN ABTEILUNG (LEITER PRIV DOZ H L KELLER) DER MEDIZINISCHEN KLINIK (DIREKTOR PROF N HENNING) DER UNIVERSITÄT ER LANGEN-NURNBERG DEUTSCHLAND

# COSTS IN DEEP THERAPY OF A 1 r TUMOUR DOSE WITH VARIOUS RADIATION SOURCES

by

HANS LUDWIG KELLER

The practice of medicine takes its origin from motives of charity usually with out regard to material considerations But in the choice of the means the physician is necessarily bound to economic considerations This applies particularly to the employment of larger technical resources as, for example costly apparatus Radiotherapy is a good example

The product, in an economic sense is usually equivalent to the financial expenditure The latter consists in the outlay for the provision of treatment rooms the purchase cost of irradiation apparatus, running costs for electricity and water, value depreciation of radiation sources and remunerations to the medical personnel

A synopsis of the initial expenditure financial outlay running costs and medical salaries is shown in Table 1

1 We have ascertained the outlay for construction of treatment rooms in cluding the necessary radiation cubicles and accessory rooms such as reception room, physician s room, office, and lavatories A life span of 25 years has been calculated for the rooms of primary importance and accordingly an annual

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**Table I**

*Financial expenditure using various radiation treatment arrangements (all the figures ex*

| | 200 kV 20 mA HVL 1 mm Cu | 300 kV 12 mA HVL 1 mm Cu | 300 kV 12 mA HVL 4 mm Cu | Cs 2 000 curie beam moving in all directions | Co 60 1 000 curie radiation in a fixed plane | Co 60 2 000 curie radiation in a fixed plane |
|---|---|---|---|---|---|---|
| *Calculated building expenses* | | | | | | |
| Treatment room | | | | | | |
| Surrounding space in m | 125 | 133 | 133 | 275 | 200 | 200 |
| Costs for 1 m surrounding space | 30 | 37 50 | 37 50 | 50 | 50 | 50 |
| Initial cost of treatment room | 3 750 | 5 000 | 5 000 | 13 750 | 10 000 | 10 000 |
| Side rooms | 5 000 | 5 000 | 5 000 | 5 000 | 5 000 | 5 000 |
| Total building expenses without special installations | 8 750 | 10 000 | 10 000 | 13 750 | 16 250 | 16 250 |
| *Initial costs of* | | | | | | |
| Apparatus and moving field treatment unit | 17 500 | 21 250 | 21 250 | 20 000 | 29 000 | 29 000 |
| Radiation source | | | | *2 500* | *5 000* | *10 000* |
| Treatment table | | | | 2 500 | 2 500 | 2 500 |
| Total initial costs without transport and custom fees | 17 500 | 21 250 | 21 250 | 25 000 | 36 500 | 41 500 |
| *Capital service per year* | | | | | | |
| Building costs | | | | | | |
| Amortization 4 % | 350 | 400 | 400 | 750 | 650 | 650 |
| Interest 5 % | *435* | *500* | *500* | *937 50* | *825* | 825 |
| Apparatus | | | | | | |
| Amortization 10 | 1 750 | 2 125 | 2 125 | 2 250 | 3 150 | 3 150 |
| Interest 5 | 875 | 1 062 50 | 1 062 50 | 1 250 | 1 875 | 2 075 |
| Wear of radiation source per year | | | | 250 | 1 000 | 2 000 |
| Rent of area and expenses for heating and lighting per year | 500 | 500 | 500 | 500 | 500 | 500 |
| Total capital service per year repairs included | 4 250 | 5 000 | 5 000 | 6 250 | 8 500 | 10 000 |
| *Operational costs* | | | | | | |
| *Tube wear expenses for electricity and cooling water per hour of radiation* | 1 dollar 13 cents | 1 dollar 25 cents | 1 dollar 25 cents | | | |
| Annual expenditure at *maximum yearly performance* | *1 425* | *1 000* | *1 750* | | | |
| *Annual salaries of staff* | 8 500 | 8 500 | 8 500 | 8 500 | 8 500 | 8 500 |
| Total sum of annual expenditure *operational costs at the theoretically* possible maximum yearly performance | 14 175 | 14 500 | 15 250 | 14 750 | 17 000 | 18 500 |

**Table 1** *(cont.)*

*cepting the first line figures representin the space required correspond to dollars and cents)*

| Co 60 2 000 curie radiation beam moving in all directions | Co 60 4 000 curie radiation beam moving in all directions | Co 60 8 000 curie radiation beam moving in all directions | 18 MeV betatron roentgen rays | 18 MeV betatron fast electrons | 35 MeV betatron roentgen rays | | 35 MeV betatron fast electrons | Linear accelerator 4 3 MeV (SL 48) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Without field homogenisation | With field homogenisation | | roentgen rays | fast electrons (theoretically) |
| 400 | 400 | 400 | 450 | 450 | 500 | 500 | 500 | 500 | 500 |
| 50 | 50 | 50 | 55 | 55 | 75 | 75 | 75 | 75 | 75 |
| 20 000 | 20 000 | 20 000 | 25 000 | 25 000 | 37 500 | 37 500 | 37 500 | 37 500 | 37 500 |
| 6 250 | 6 250 | 6 250 | 7 500 | 7 500 | 7 500 | 7 500 | 7 500 | 7 500 | 7 500 |
| 26 250 | 26 250 | 26 250 | 32 500 | 3[illegible] 500 | 45 000 | 45 000 | 45 000 | 45 000 | 45 000 |
| 42 500 | 47 500 | 47 500 | 112 500 | 112 500 | 185 500 | 185 500 | 185 500 | 150 000 | 150 000 |
| 10 000 | 20 000 | 40 000 | | | | | | | |
| 2 500 | 2 500 | 2 500 | | | | | | | |
| 55 000 | 70 000 | 90 000 | 112 500 | 112 500 | 185 500 | 185 500 | 185 500 | 150 000 | 150 000 |
| 1 050 | 1 050 | 1 050 | 1 300 | 1 300 | 1 550 | 1 550 | 1 550 | 1 550 | 1 550 |
| 1 312.50 | 1 312 50 | 1 312 50 | 1 625 | 1 625 | 2 250 | 2 250 | 2 250 | 2 250 | 2 250 |
| 4 500 | 5 000 | 5 000 | 11 250 | 11 250 | 18 550 | 18 550 | 18 550 | 15 000 | 15 000 |
| 2 750 | 3 500 | 4 500 | 5 625 | 5 625 | 9 250 | 9 250 | 9 250 | 7 500 | 7 500 |
| 2 000 | 4 000 | 8 000 | | | | | | | |
| 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| 12 500 | 15 750 | [illegible]0 375 | 21 250 | 21 250 | 33 750 | 33 750 | 33 750 | 28 750 | 28 750 |
| | | | 11 25 $ | 11 [illegible]5 $ | 3 75 $ | 3 75 $ | 3 75 $ | 1 75 $ | 1 75 $ |
| | | | 10 000 | 3 750 | 3 250 | 4 500 | 8[illegible]5 | 1 125 | 1 125 |
| 8 500 | 8 500 | 8 500 | 10 500 | 10 500 | 10 500 | 10 500 | 10 500 | 10 500 | 10 500 |
| | | | | | Technical staff | | | 2 000 | 2 000 |
| 21 000 | 24 250 | 8[illegible] | 41 [illegible]0 | [illegible]00 | 47 500 | 48 750 | 45 000 | 42 375 | 42 375 |

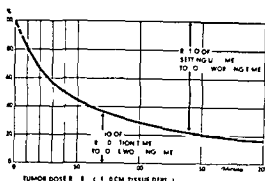


Fig 1 Relationship of preparation time to irradiation time depending upon the tumour dose rate single tumour doses of 250 r in 10 cm tissue depth preparation time 6 3 min

depreciation in value of 4 % Interest at 5 % on the initial funds was also taken into consideration The internal area of the treatment room was calculated at 25 m²

2 For the radiation sources and irradiation apparatus an average life of 10 years and therefore an annual depreciation of 10 %, and an annual interest at 5 % on the purchase price, were selected

3 The running costs, i e costs of electricity (about 2 5 cents per kilowatt) and cooling water (about 12 cents per m³), as well as wear and tear of radiation sources are about proportionally dependent on the number of working hours An overall sum for recurring costs, such as for heating and lighting of the rooms also has to be included The expenditures for writing material forms, and patient statistics may apparently be neglected

4 Essential items are the salaries and wages of the treatment personnel For the operation of a full time irradiation unit the costs were estimated as follows

| | |
|---|---|
| Annual expenditure for 1 assistant radiologist | $ 4 000 |
| Annual combined expenditure for 1 1/2 technical assistants | $ 3 500 |
| Share of typist 1/2 salary per annum | $ 600 |
| Share of cleaning 1/3 salary per annum | $ 400 |
| In all | $ 8 500 |

These expenses for personnel are about the same with fully worked apparatus for deep therapy of conventional construction and with radioactive isotopes as radiation source In the case of various particle accelerators a further amount must be added for technical personnel

A physicist does not appear to be indispensable, but for the linear accelerators and the betatrons it is necessary to employ well trained personnel Accordingly, for such medical personnel an annual expenditure of $ 10 500 in toto was arrived at

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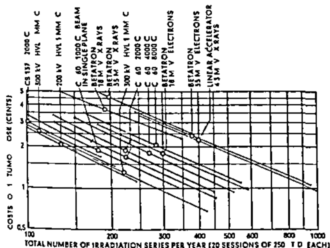



Fig 2 Comparison of the yearly performance and costs of 1 r tumour dose using various sources of radiation The continuous curves show the range of yearly performance from cost standpoint between 25 % and 75 % fulfilment of the maximum yearly performance theoretically possible A circle on the curve marks a 40 fulfilment

The roentgen tumour dose corresponds economically to the means produced by the costs Health insurance companies in various countries take the superficial dose as the basis for calculation of the fee for deep therapy but this is apt not to compensate for the best qualitative results for example, deep therapy with low energy radiation must obviously be in a different category from treatment with ultra hard radiation In the present consideration it is therefore the dose applied to the tumour that is made the focus of the economic evaluation

The number of working hours is on the whole a constant The working year consists of about 50 weeks each of 40 working hours and therefore amounts to 2 000 working hours In this period of time only a certain number of treatments can be carried out The time allotted to the treatment of each individual may be divided into a so called preparation time and the treatment time itself In the preparation time the patient is brought into the room undressed positioned upon the table and the treatment field set up after the treatment he is dressed and taken from the room It would appear that the preparation time is a little over 6 minutes Our average value with always the same medical personnel is generally constant on the other hand the treatment time depends upon the tumour dose rate of the apparatus used

The relation between preparation time and treatment time is therefore equivalent to the relation between a constant and a variable quantity It is illustrated in the first graph (Fig 1) with the percentage proportion of treatment time to the total working time on the ordinate and the various tumour dose rates taken at an average depth of 10 cm on the abscissa It will be seen that

**Table 2**

*Comparison of accomplished tumour doses by various radiation units*

| | 200 kV 20 mA HVL 1 mm Cu | 300 kV 12 mA HVL 1 mm Cu | 300 kV 12 mA HVL 4 mm Cu | $^{137}$Cs 2 000 C beam moving in all directions | $^{60}$Co 1 000 radiation — At commencing activity |
|---|---|---|---|---|---|
| Free air dose (r/min) (50 cm focus to chamber distance) | 70 | 200 | 45 | 30 | 78 |
| Relative depth dose in of free air dose for roentgen rays in 10 cm tissue depth *for fast electrons according to energy* | 30 % | 30 | 38 | 43 | 49 % |
| Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given) | 21 0 r/min | 60 r/min | 17 r/min | 13 r/min | 38 r/min |
| Hours of radiation per year of 2 000 working hours | 1 300 hours | 800 hours | 1 360 hours | 1 540 hours | 1 000 hours |
| Tumour dose at maximum yearly performance in 10 r | 1 64 | 2 9 | 1 4 | 1 2 | 2 3 |
| Treatment series per year à 20 × 250 r tumour dose | 328 | 580 | 280 | 240 | 460 |
| Single treatments per year à 250 r tumour dose | 6 560 | 11 600 | 5 600 | 4 800 | 9 200 |
| Single treatments à 250 r per working day (1 year = 260 working days) | 25 | 44 5 | 21 5 | 18 5 | 35 5 |
| Costs of 1 r tumour dose at 100 utilization of the theoretically possible maximum yearly performance (Amer cents) | 0 875 | 0 5 | 1 1 | 1 23 | 0 7 |
| Costs of 1 r tumour dose at 40 utilization of the theoretically possible maximum yearly performance (Amer cents) | 2 1 | 1 2 | 2 65 | 2 95 | 1 68 |

at a tumour dose rate of about 38 r/min, the preparation time is equal to the irradiation time At smaller dose rates the treatment time predominates, and for larger dose rates the preparation time is greater It therefore follows that in a working year of 2 000 hours at high dose rates a relatively short irradiation time is required compared with a relatively long time with small tumour dose rates This may be exemplified as follows

At a tumour dose rate of 62 r/min the working year consists of 800 irradiation

**Table 2** *(cont )*

*(See also pp 376—377 for horizontal continuation of table)*

| C fixed plane | $^{60}$Co 2 000 C fixed radiation plane | | Co 2 000 C beam moving in all directions | | $^{60}$Co 4 000 C beam moving in all directions | |
|---|---|---|---|---|---|---|
| By half l fe | At com mencing activity | By half life | At com mencing activity | By half life | At com mencing activity | By half life |
| 39 | 144 | 72 | 144 | 72 | 260 | 130 |
| 49 | 49 | 49 ° | 49 | 49 | 49 | 49 ° |
| 19 r/min | 70 r/min | 35 r/min | 70 r/min | 35 r/min | 128 r/min | 64 r/min |
| 1 340 hours | 740 hours | 1 040 hours | 740 hours | 1 040 hours | 480 hours | 760 hours |
| 1 53 | 3 1 | 2 2 | 3 1 | 2.2 | 3 7 | 2 95 |
| 306 | 620 | 440 | 620 | 440 | 740 | 590 |
| 6 120 | 12 400 | 8 800 | 12 400 | 8 800 | 14 800 | 11 800 |
| 24 | 48 | 34 | 48 | 34 | 57 | 45 |
| 1 12 | 0 6 | 0 83 | 0 65 | 0 95 | 0 6[illegible] | 0 83 |
| 2 7 | 1 44 | 2 0 | 1 56 | 2 27 | 1 58 | 2 0 |

hours, whereas at a tumour dose rate of 17 r/min the working year is increased to 1 360 irradiation hours Consequently in order to achieve twice the number of treatments during a working year for example it is not sufficient to double the tumour dose rate it must be increased to more than 4 times its value Moreover, it is clear that each treatment unit can only achieve a certain number of tumour series per year, and this depends upon the average tumour dose rate (See Table 2 )

Table 2 *(cont.)*

| | $^{60}$Co 8 000 C beam moving in all directions | | 18 MeV betatron roentgen rays | |
|---|---|---|---|---|
| | At commencing activity | By half life | Without field homogenisation | With field homogenisation |
| Free air dose (r/min) (50 cm focus-to-chamber distance) | 500 | 250 | 80 | 65 |
| Relative depth-dose in % of free air dose for roentgen rays in 10 cm tissue depth for fast electrons according to energy | 49 % | 49 % | 63 % | 63 |
| Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given) | 196 r/min | 98 r/min | 50 r/min | 35 r/min |
| Hours of radiation per year of 2 000 working hours | 200 hours | 280 hours | 880 hours | 1 080 hours |
| Tumour dose at maximum yearly performance in 10 r | 4 0 | 2 8 | 2 65 | 2 3 |
| Treatment series per year à 20 × 250 r tumour dose | 800 | 560 | 530 | 460 |
| Single treatments per year à 250 r tumour dose | 16 000 | 14 000 | 10 600 | 9 200 |
| Single treatments à 250 r per working day (1 year = 260 working days) | 80 | 70 | 41 | 35 |
| Costs of 1 r tumour dose at 100 utilization of the theoretically possible maximum yearly performance (Amer. cents) | 0 73 | 0 93 | 1.58 | 1 8 |
| Costs of 1 r tumour dose at 40 utilization of the theoretically possible maximum yearly performance (Amer. cents) | 1 76 | 2 25 | 3 6 | 4.25 |

The cost of 1 r tumour dose may be given by a certain figure only when a fixed number of patients are treated per annum. Strictly speaking the relationship can be shown only by means of a cost performance graph (Fig. 2). This gives the costs per 1 r tumour dose in cents on the ordinate and the number of applied tumour series per annum on the abscissa. The continuous curves indicate the cost range of yearly performance between a 25 % and 75 % utilization of the theoretically possible maximum annual performance. A circle on

**Table 2** *(cont.)*

| 18 MeV betatron fast electrons | 35 betatron roentgen rays | | 35 MeV betatron fast electrons | Linear accelerator 4 to 6 MeV | |
|---|---|---|---|---|---|
| | Without field homogen isation | With field homogen isation | | Roentgen rays | Fast electrons (theoreti cally) |
| 300 | 75 | 40 | ca 500 | 400 | ca 500 |
| | focus-to-chamber-distance 1 m | | | focus-to-chamber-distance 1 m | |
| ca. 100 | 65 % | 65 % | ca. 100 % | 60 % | ca 100 % |
| ca 250 r/min | 50 r/min | 26 r/min | 500 r/min | ca 250 r min | ca 500 r min |
| ca. 400 hours | ca 860 hours | 1 [illegible]00 hours | ca 400 hours | ca 400 hours | ca 400 hours |
| 4.5 | 2.6 | 1.88 | 4 8 | 4 8 | 4 8 |
| 900 | 5[illegible]0 | 375 | ca 1 000 | ca 1 000 | ca. 1 000 |
| 18 000 | 10 400 | 7 500 | ca 20 000 | ca 20 000 | ca. 20 000 |
| 69 | 40 | 29 | ca 80 | ca 80 | ca 80 |
| 0.786 | 1.82 | [illegible]6 | 0 95 | 0 875 | 0 875 |
| 1.88 | 4 36 | 6.25 | 2 3 | 2 1 | 2.1 |

the curves marks the 40 % accomplishment of the maximum yearly perform ance The costs of a 1 r tumour dose at an average utilization of the effi ciency of the radiation sources may thus be calculated Modern radiation units necessitating a relatively high initial expenditure mostly compensate for this extra cost by an increase in the yearly work performance This applies particularly to the cobalt 60 sources to the linear accelerators and to the betatrons especially if employed as electron generators If betatrons are

Table 2 *(cont.)*

| | $^{60}$Co 8 000 C beam moving in all directions | | 18 MeV betatron roentgen rays | |
|---|---|---|---|---|
| | At commencing activity | By half life | Without field homogenisation | With field homogenisation |
| Free air dose (r/min) (50 cm focus-to-chamber-distance) | 500 | 250 | 80 | 65 |
| Relative depth-dose in % of free air dose for roentgen rays in 10 cm tissue depth for fast electrons according to energy | 49 % | 49 % | 63 % | 63 |
| Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given) | 196 r/min | 98 r/min | 50 r/min | 35 r/min |
| Hours of radiation per year of 2 000 working hours | 200 hours | 280 hours | 880 hours | 1 080 hours |
| Tumour dose at maximum yearly performance in $10^6$ r | 4.0 | 2.8 | 2.65 | 2.3 |
| Treatment series per year à 20 × 250 r tumour dose | 800 | 560 | 530 | 460 |
| Single treatments per year à 250 r tumour dose | 16 000 | 14 000 | 10 600 | 9 200 |
| Single treatments à 250 r per working day (1 year = 260 working days) | 80 | 70 | 41 | 35 |
| Costs of 1 r tumour dose at 100 % utilization of the theoretically possible maximum yearly performance (Amer. cents) | 0.73 | 0.93 | 1.58 | 1.8 |
| Costs of 1 r tumour dose at 40 % utilization of the theoretically possible maximum yearly performance (Amer. cents) | 1.76 | 2.25 | 3.[illegible] | 4.25 |

The cost of 1 r tumour dose may be given by a certain figure only when a fixed number of patients are treated per annum. Strictly speaking the relationship can be shown only by means of a cost performance graph (Fig. 2). This gives the costs per 1 r tumour dose in cents on the ordinate and the number of applied tumour series per annum on the abscissa. The continuous curves indicate the cost range of yearly performance between a 25 % and 75 % utilization of the theoretically possible maximum annual performance. A circle on

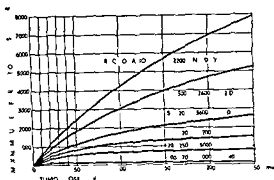


Fig 4 Theoretical maximum performance of treatment series per year (for a working year of 2 000 hours) depending upon the tumour dose rate for various fractionations with biologic equivalent effect on the tumour (from ANDREWS & MOODY)

The cost consideration in the choice of radiation technique and fractionation is of particular interest

In order to apply a tumour dose of 5 000 r in single surface doses of 250 r using the stationary field and cross fire technique according to the choice of radiation and the various relative depth doses 66 to 31 single treatments are required, as opposed to 20 treatments with moving field therapy To obtain the same tumour dose therefore, the stationary field method leads to higher fractionation

Such a fractionation involves a considerable average reduction of 0 66 times the yearly performance, as may be seen from Fig 4 Providing there is a sufficiently high number of available cases this results in a 50 % cost increase for a 1 r tumour dose Apart from the clinical point of view economic considerations therefore become critical factors in the argument that moving field therapy is to be preferred to the stationary field technique

## SUMMARY

The annual expenses of radiation deep therapy (cost of buildings and plant and running expenses and salaries of staff) are considered in relation to the possible tumour dose rate (at 10 cm tissue depth) with various types of apparatus These would appear to vary to a marked degree in various centres Tables are shown from which variations according to local circumstances may be derived It is evident that the relatively high cost of elaborate apparatus may often be offset by the large number of cases possible to treat

## ZUSAMMENFASSUNG

Es wird der Jahresaufwand für die Strahlentiefentherapie (Kosten für Gebäude Bestrahlungseinrichtungen Betriebsmittel und Personal) gegenübergestellt der möglichen Dosisleistung am Herd (in 10 cm Gewebetiefe) pro Jahr bei verschiedenen Tiefentherapiegeräten Die Ar

beit ist sich bewußt dass in der Welt die Kosten sehr verschieden sind Es werden daher Tabellen gezeigt die nach den lokalen Verhaltnissen variiert werden konnen Bei Apparaturen mit hohem Anschaffungspreis wird haufig infolge der wesentlich hoheren Dosisleistung ein viel grosseres Patientengut bewaltigt


## RÉSUMÉ

L auteur a déterminé d une part le coût annuel de la thérapie profonde par les radiations (coût des bâtiments et des appareils d irradiation frais de fonctionnement et salaires) et d autre part la dose à la tumeur (à 10 cm de profondeur) que peuvent émettre annuellement divers types d appareillages de thérapie profonde Les frais peuvent varier beaucoup d un pays a l autre L auteur publie des tableaux que l on peut adapter à ces facteurs locaux Souvent les appareils dont le prix d achat est élevé ont une capacité de fonctionnement annuel notablement plus grande permettant de traiter beaucoup plus de malades


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# BOOK REVIEWS

IONIZING RADIATION AN OLD HAZARD IN A NEW ERA. By George Tievsky 154 pages 63 illustrations and 5 tables Charles C Thomas Springfield Ill 1962 Price $ 8

The physical radiobiologic and genetical background to the understanding of various kinds of radiation hazards are first presented in a simplified and sometimes not too accurate manner In the two chapters on fluoroscopy and radiography the author stresses the importance to limit as far as possible whitout jeopardizing the diagnostic results the radiation doses received by patients and personnel He gives the more important rules to follow for this end These rules should already be well known and applied it is to hoped by all radiologists but surgeons and others using roentgen radiation and without special training in radiology should study them closely The author rightly advises non radiologists to refrain from more specialized and difficult roentgen examinations because of lack of experience they will usually inflict unnecessarily high doses on their patients and themselves and with inferior diagnostic result There is no special chapter on radiotherapy

The irradiation of human beings in general by natural radioactivity and by radioactive fall out is then discussed and some comparisons of magnitudes are presented in order to retain a sense of proportions Some figures are contained in an appendix by G M Dunning Legal considerations are stressed such as the difficulty in many cases of deciding whether a workman s compensation claim for radiation injury is warranted as well as the impossibility of founding a future policy in all questions of radiation protection solely on scientific facts A judgment of values is also necessary to ensure that the positive consequences of a proposed policy weigh over the negative ones Finally some information is given on national and international bodies considering radiation hazards on Handbooks of the National Bureau of Standards and a glossary of terms is presented

In short the book constitutes a popular and readable presentation of a subject of great topical interest although parts of it should be taken with a grain of salt A study of the references quoted should be helpful in this respect

*Sten Benner*

DIE WIRBELSÄULE IN DIAGNOSTIK UND THERAPIE Verhandlungen der 2 Arbeitstagung der Gesellschaft fur Wirbelsaulenforschung 1961 in Frankfurt am Main 208 Seiten 79 Abbildungen Hippokrates-Verlag Stuttgart 1962. Price 39 DM

This book reports on 35 congress papers Some of the papers dealing with radiography of the vertebral arteries performed on cadavers in the course of which the blood flow at different rotations of the spine was experimentally studied are of particular interest to radiologists The clinical significance of this mechanical influence is discussed in the light of similar studies in patients

The lectures are of general and theoretical interest but they do not from the purely radiologic viewpoint provide much new information

*Folke Knutsson*

I Internationaler Kongress für Medizinische Photographie und Kinematographie Herausgegeben von H Orbach 362 Seiten und 275 Abbildungen Georg Thieme Stuttgart 1962 Price 88 DM

The first International Congress of Medical Photography and Cinematography was held at Dusseldorf in September 1960 the transactions have now been beautifully printed in a handy volume containing about 140 papers Many subjects from the wide field of photography are of interest to a radiologist although some of them will be well known from recent radiologic meetings Some technical papers particularly those on modern roentgen films and their properties and on processing machines will also prove of value Parts of the papers on image quality obtained with the image amplifier and on problems connected with television and cinefluorography memory tubes and the microroentgen technique have been published previously

Of probably less account to the radiologist are the communications on endoscopic ophthalmologic dental orthopedic and surgical photography Fluorescence photography (for skin diseases) and electron microscopy are also dealt with and general medical photography educational films and the standardization of photography in hospitals are discussed Cinematography in different connections is comprehensively covered

The comments in the accompanying discussions at least those that have been published are surprisingly few The reviewer regrets that the author of the paper on the possibilities of reducing dosage by increasing the development temperature seems to have overlooked certain important elementary physical facts

*Ove Mattsson*

Strahlenschutz in Forschung und Praxis Band I Jahrbuch der Vereinigung deutscher Strahlenschutzarzte Herausgegeben von H J Melching 252 Seiten 93 Abbildungen und 31 Tabellen Rombach Freiburg im Breisglau 1962 Price DM 39

Lectures covering a survey of selected topics during a radiation protection course to German physicians in January 1961 are collected in this book The interests of those actually working with radiation of those exposed as patients during radiologic examinations and treatments and of third parties are considered The report of H Holthusen on the extensive investigation of patient doses in Hamburg in which about 1 4 million examinations and treatments are analyzed is of special interest Holthusen and other authors stress the importance of improving methods in common use and the possibility substantially to reduce patient doses without sacrificing the medical value of examinations

Other papers describe various forms of radiation injury and the treatment in such cases as well as waste disposal in atomic energy and medical isotope work The German legal aspects of radiation protection appear to be of limited value to readers in other countries although questions of general interest are also discussed in these communications e g the difficulty or impossibility of proving in a given case the causal relationship between irradiation and injury especially when the latter is delayed This naturally limits the chance of the injured party obtaining compensation from the responsible authority

*Sten Benner*

Whole body Counting Proceedings of a symposium held by the International Atomic Energy Agency Vienna 12—16 June 1961 535 pages International Atomic Energy Agency Vienna 1962 Price 3 £ (in North America 10 00 $)

The measurement of low level radio-activity in the human body is a field of study requiring considerable skill and care in the design of apparatus in the performance of measurements and in the interpretation of the results If these conditions are fulfilled valuable information on radio-active fall-out distribution and metabolism may be obtained It is further possible to perform several diagnostic radio-isotope studies with a much smaller quantity of radio-activity than in ordinary methods or to follow the excretion of a given dose over a longer period of time The measurement of natural radio-activity in the body is also often of clinical interest

A debt of gratitude is therefore owed to the International Atomic Energy Agency for convening a meeting of prominent scientists from several countries and for publishing the proceedings in the present volume containing 33 papers mostly in English but 5 of them in French Various types of detectors calibration methods typical measurement facilities and data processing techniques are described Some devices for measuring the activity in part of the body or for studying the activity distribution are also mentioned

Certain papers concern the measurement of natural radio-activity from which potassium content and lean body mass may be estimated others which cannot be reviewed in detail give several examples of the advantages accruing from the use of low level counting methods for various diagnostic tests

The book should be of great interest to all workers in the field and its value is enhanced by the summaries of discussions which give much useful supplementary information

*Sten Benner*

Molecular Biophysics By Richard B Setlow and Ernest C. Pollard 545 pages 258 illustrations and 52 tables Pergamon Press Oxford 1962 Price 84 Sh

This book gives an account of the various physical and chemical methods in use for studying the structure and properties of biologically important complicated organic molecules (diffusion sedimentation birefringence absorption spectra roentgen ray diffraction electron spin resonance) It further reviews cellular biology in general and commonly used methods such as light and electron microscopy isotopic tracer methods radiation effects on viruses enzymes cells and especially chromosomes) One chapter gives applications in muscle nerve and eye physiology Most of the chapters end by a number of problems for the reader

The book contains a wealth of factual matter and interesting discussions on important topics especially from the physicist s point of view It does not always provide easy reading but is well worth a thorough study by anyone who wants to penetrate the problems dealt with or who is already active in the field The chapters dealing with radiation effects and isotopic tracer methods would seem to be of greatest interest to the readers of this Journal

*Sten Benner*

Einfuhrung in die Messtechnik der Kernstrahlung und die Anwendung der Radioisotope 2 Auflage Herausgegeben von H Fassbender 420 Seiten 244 Abbildungen und 26 Tabellen. Georg Thieme, Stuttgart 1962 Price 49 50 DM

The first edition of this book was described by the present reviewer as being probably of more interest to technical than to medical readers The second edition has been considerably enlarged and is the work of specialists in the various fields and now no longer written by one author Medical questions are however still treated relatively briefly emphasis being placed on radiation measurements and the design of the necessary instruments The book seems to be of particular interest to instrument designers and those concerned with the technical uses of radioisotopes

*Sten Benner*

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# AUTORADIOGRAPHY OF VARIOUS RAT TISSUES AFTER THE ADMINISTRATION OF BISMUTH 210

by

C J H VAN DEN BROEK

The use of $^{206}$Bi as a radiation source in the detection and therapy of neoplastic diseases has been investigated by VAN DER WERFF (22 23 ) In the course of this work it was thought desirable to collect more detailed information on the distribution of bismuth in various organs and tissues Autoradiography is the usual method of choice for this kind of information However $^{206}$Bi being a pure $\gamma$ emitter is unsuitable for anything but the roughest localization Thus VAN DER WERFF & HAANEN (24) who used $^{206}$Bi absorbed on coal particles and injected this into leucemic patients obtained only a vague contact autoradiogram of its accumulation in a lymph node

Bismuth 210 on the other hand decays with a half life of 5 0 days with emission of 1 17 MeV $\beta$ rays into $^{210}$Po this in turn decays with a half life of 140 days with emission of both $\alpha$ (5 3 MeV) and $\gamma$ rays into stable $^{206}$Pb Whereas the mean $\beta$ energy of $^{210}$Bi is rather high for accurate localization in autoradiograms the $\alpha$ particles of polonium produce short straight tracks in a photographic emulsion which can be traced down even to individual cells A sharp localization of bismuth is therefore possible by injecting a preparation of freshly isolated $^{210}$Bi into a test animal fixing its tissues after a time interval

From the Department of Histology Faculty of Medicine University of Utrecht the Netherlands Submitted for publication 10 January 1963

short in comparison with the half life of $^{210}$Bi, storing the dehydrated tissues in paraffin blocks for some 4 to 5 of these half lives and studying in autoradiograms the distribution of the $\alpha$ tracks originating from the $^{210}$Po that has developed from practically all the $^{210}$Bi during the storage interval. LACASSAGNE & FOUCAULD (6) in the early thirties demonstrated the presence of bismuth in various organs by this method and later KAHN (5) recorded its presence in tumours. Since then the autoradiographic technique has been markedly improved (ref. 20) and its resolution brought down to the cellular level.

The method has the disadvantage that a time interval between the isolation of $^{210}$Bi and its administration to the animal, and between the latter and the fixation of the tissues, is unavoidable. Whereas the first period can be reduced to a minimum, the second is inherent to the experiment. It was thought, however, that the 13 per cent of $^{210}$Bi that turned into $^{210}$Po within the first 24 hours after administration would not seriously impair a demonstration of a possibly specific accumulation of bismuth.

In the present experiment the preparation and injection of $^{210}$Bi, as well as all work on the tissues up to their embedding in paraffin were carried out at the St. Canisius Hospital, Nijmegen, Holland, under the supervision of Mr. VAN DER WERFF, upon the request of whom the preparation and evaluation of the autoradiograms were carried out by the present author.

*Materials and Methods.* $^{210}$*Bi, as a* $BiCl_3$ *solution, was obtained from Philips* Duphar, Amsterdam. The vena saphena of 5 ordinary white rats of approximately 200 g bodyweight was injected with 1 ml neutral saline prepared to contain 0.1, 0.3, 1, 3, and 10 $\mu$C respectively; these doses correspond with the range from tracer dose to therapeutic dose in man. The 5 animals, together with a control, were killed after 24 hours, and the liver, lung, kidney, spleen and bone marrow (sternum) were immediately fixed in 10 % formaldehyde solution and embedded in paraffin wax according to usual practice. The exact time interval between the preparation of the batch of $^{210}$Bi and the injection of the animals was unfortunately not registered, so that the injected solution contained more than the unavoidable minimum of polonium. Although this would undoubtedly diminish the exactitude, it was thought that some of the results were sufficiently clear to warrant this report, the more so as the said time interval was reported to be considerably shorter than the half life of bismuth and hence the contamination by polonium considerably less than 50 per cent (VAN DER WERFF).

Between 20 and 35 days after fixation, 3$\mu$ and 7$\mu$ sections were prepared and autoradiograms obtained by the application of Kodak AR. 10 stripping film in the usual manner (ref. 1, 20). The exposure time for most preparations varied between 3 and 12 weeks; for bone marrow this was extended to 22 weeks because of the rather low radioactivity and small available tissue areas.

**Table 1**

*Radioactivities of various tissues as percentages of the highest radioactivity*

| Injection prepared to contain | 0 1 μC | 0 3 μC | 1 μC | 3 μC | 10 μC | Mean |
|---|---|---|---|---|---|---|
| *Kidney* tubuli | 100 | 100 | 100 | 100 | 100 | 100 |
| glomeruli | 51 7 | 87 8 | 111 2 | 79 4 | 64 7 | 79 0 |
| *Spleen* red pulp | 34 2 | 55 6 | 38 8 | 48 5 | 30 6 | 41 5 |
| white pulp | 26 6 | 37 5 | 36 2 | 36 3 | 25 0 | 32 3 |
| *Liver* periportal area | 18 6 | 30 2 | 18 6 | 33 9 | 17 9 | 23 8 |
| parenchyma | 17 1 | 31 9 | 15 6 | 18 5 | 19 9 | 20 6 |
| vena centralis | 22 9 | 23 4 | 13 6 | 14 1 | 14 8 | 17 7 |
| *Bone marrow* | 11 4 | 19 2 | 14 6 | 11 6 | 13 3 | 14 0 |
| *Lung* parenchyma | 6 0 | 22 9 | 11 6 | 10 8 | 10 3 | 12 3 |
| *Kidney* medulla | 13 0 | 13 6 | 8 3 | 6 1 | 6 0 | 9 4 |

Notwithstanding its limited thickness of 5μ, the stripping film, after development in Kodak D19b at 18 C for 5 min and fixation, showed very clear α tracks which were subsequently evaluated in the following two ways

1 Homogeneous tissue areas were sought in autoradiograms made from 7 μ sections stained with methyl green and pyronine and showing suitable track densities, their surfaces were measured from camera lucida drawings and the number of tracks counted After due corrections for radioactive decay exposure time and background (negligible for tracks) comparable figures were arrived at for the number of tracks per 10 000 μ tissue area per unit exposure time Figures, derived from preparations from one tissue after different times of exposure, generally agreed within 20 to 30 per cent with some exceptions in cases of low track density

2 Similar homogeneous tissue areas were sought and systematically searched with an oil immersion objective in autoradiograms from 3 μ sections stained with Mayer s hemalum The origin of the type of cell was registered in at least 200 α tracks The track distribution thus found was then compared with a chance distribution obtained by registering the cells on which a black dot mounted in the microscope ocular fell in at least 200 chance positions of the preparation (point hit method)

## Results

1 *Quantitative* All tissues studied gave a measurable number of tracks in the autoradiograms but in all animals striking variations in track density between tissues or tissue components were observed Moreover the relative radioactivities of the various tissue components were found to be essentially similar for all doses administered These relative radioactivities expressed as

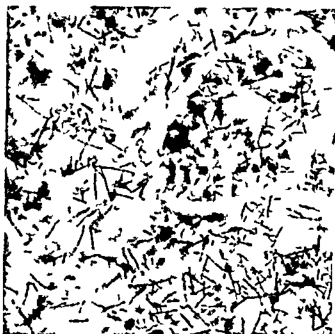


Fig 1 α track autoradiogram of rat renal cortex fixed 24 hrs after administration of 10 μC Bi chloride Very high track density over proximal convoluted tubules less in glomerulus

percentages of the track density of the tissue component with the highest incorporation i e renal tubules (with one minor exception) are presented in Table 1 Tissue components are arranged in the table in the order of decreasing radioactivity, and the similarity of this order permits its expression in the mean percentages given in the last column

It is apparent from these figures that 24 hours after injection of any dose between 0 1 and 10 μC there is a marked concentration of the isotope(s) in the renal tubuli and only little less in the glomeruli (in the latter supposedly in the process of excretion) The renal cortex as a whole always contains about ten times as much isotope as the renal medulla Isotope concentration in the spleen, though still prominent is much lower, and the radioactivity of the red pulp is consistently somewhat higher than that of the white pulp It is surprising to find no significant difference between the parenchyma and the periportal areas of the liver The track numbers for the venae centrales apply only to tracks evident in the lumina of these vessels, inside as well as outside the blood cells It is obvious, especially when comparison is made with the figures for the renal medulla, that the liver accumulates the *isotope*, albeit in a lesser degree than the renal cortex This accumulation stands out more clearly when other tissues are also taken into account Incidental but less complete countings performed for muscle and bone reveal a track density in

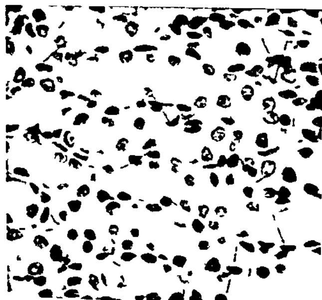


Fig 2 Autoradiogram of rat renal medulla fixed 24 hrs after administration of 10 $\mu$C $^{210}$Bi chloride Same exposure time as in fig 1 hence track densities comparable

these tissues of the same order of magnitude as in the renal medulla and thus noticeably weaker than in the liver The approximation of the counts for the hepatic parenchyma periportal areas and venae centrales may indicate that 24 hours after injection there is still a marked transport of isotope in the liver

The figures for the lung are much lower than those for the liver but as only a part of the pulmonary areas evaluated represents tissue proper the track count for the latter may well be in the same order of magnitude as that for the liver The low figures for bone marrow are unexpected especially in relation to those for the spleen These figures have however been checked in a fair number of additional preparations

The ratios of tissue radioactivity are given for each tenfold increase in dose in Table 2 With some exceptions which must be ascribed to the low track numbers obtained from the 0 1 $\mu$C dose most of these ratios are seen to lie between 5 and 7 Hence for all tissues the increase in radioactivity is approximately proportional to the injected dose Notwithstanding the apparent accumulation of isotope in some organs radioactivity in most tissues increases 5 to 7 times for each tenfold increase in dose over the entire range from 0 1 to 10 $\mu$C

As far as deviations from this general rule can be observed it might seem that the ratios are lowest for the less radioactive tissues This would imply

**Table 2**

*Track count ratios for a 10:1 increase in dose*

| Dose ratio | 100:1 | 300:3 | 1000:10 | Mean |
|---|---|---|---|---|
| *Kidney* tubuli | 5.9 | 9.9 | 5.8 | 7.2 |
| glomeruli | 12.6 | 8.9 | 3.4 | 8.3 |
| *Spleen* red pulp | 6.6 | 8.6 | 4.6 | 6.6 |
| white pulp | 8.0 | 9.5 | 4.0 | 7.2 |
| *Liver* periportal area | 5.8 | 11.0 | 5.6 | 7.5 |
| parenchyma | 5.3 | 5.7 | 7.4 | 6.1 |
| vena centralis | 3.5 | 5.9 | 6.3 | 5.2 |
| *Bone marrow* | 7.5 | 5.9 | 5.3 | 6.2 |
| *Lung* parenchyma | 11.3 | 4.7 | 5.2 | 7.1 |
| *Kidney* medulla | 3.7 | 4.5 | 4.2 | 4.1 |
| Mean | 7.0 | 7.5 | 5.2 | 6.6 |

that the capacity of the actively accumulating tissues has not been overloaded by the higher doses of isotope.

Finally, as all counts were derived from tissue sections of identical thickness, the relative radioactivities given in Table 1 may also be regarded as the relative isotope dose per unit volume of these tissues. They may assist in furnishing an idea of the radiation damage to be expected in these tissues during the first day after injection of $^{206}$Bi chloride.

2. *Qualitative.* The qualitative evaluation of the autoradiograms, for which over 5 000 tracks were traced down to individual cells, showed that the track distribution in the great majority of cases coincided closely with a random distribution recorded by the point hit method.

The cells of the proximal convoluted tubules in the renal cortex only (see Fig. 1) had an accumulation of tracks far in excess of the random distribution. It is predominantly by these cells that the isotope or isotopes are accumulated within the first 24 hours after injection. The track density in the distal convoluted tubules was judged to be only little in excess of that in the renal medulla where it was very low (see Fig. 2). The far more numerous tracks in the glomeruli again showed an essentially random distribution.

Seven per cent of the tracks in the spleen of two of the five animals were traced down to macrophages against 3 per cent random hits. Owing to the relative scarcity of these cells no more than 96 tracks have been attributed to them, but this number seems sufficient to explain them as a sign of some accumulation by these cells.

No significant accumulation could be detected in the Kupffer cells of the liver. Conversely, if these cells should have accumulated isotope to any marked



Fig 3 Autoradiogram of rat lung fixed 24 hrs after administration of 10 μC $^{210}$Bi chloride Tracks are present likewise over lung parenchyma and arterial media

degree, it would certainly have been noted amidst the rather low overall track density

Tracks over various tissue components of the lung are depicted in Fig 3 to illustrate the random distribution in other tissues

## Discussion

Neither the distribution of tracks at the organ level nor that at the cellular level show any variations corresponding with the 1 100 variation in the administered dose This would mean that even the largest dose (equivalent to a therapeutic dose in human subjects, as previously mentioned) is not large enough to disturb the distribution to any marked degree within the first 24 hours after injection It remains of course to be seen whether the influence of an isotope dose would (quite aside from a difference in radiation damage) become noticeable at longer intervals

There seems to be some contradiction between the qualitative and the quantitative results described above The former clearly point to a specific accumulation of isotope by some tissues especially the renal cortex and spleen but in the latter such specificity is much less marked at the cellular level where only the proximal tubules of the kidney and less definitely the macrophages of the spleen display signs of accumulation

**Table 3**

*Comparison of relative radioactivities in rat and mouse organs 24 hours after the administration of radioactive Bi in aqueous solution in various experiments*

| Authors | Ref | Compound | Animal | Kidney | Spleen | Liver | Lung | Bone marrow |
|---|---|---|---|---|---|---|---|---|
| PASSALACQUA | 16 Table 2 | $^{206}$Bi nitrate | Rat | 100 ∧ | 0.5 > | 1.5 > | 0.5 > | — |
| PASSALACQUA | 17 Table 2 | $^{206}$Bi nitrate | Mouse* | 100 = | 4.1 < | 8.2 > | 4.1 = | — |
| PASSALACQUA | 17 Table 3 | $^{206}$Bi nitrate | Rat* | 100 < | 20 > | 5 < | — | 25 < |
| PASSALACQUA & KOCH | 19 Table 3 | $^{206}$Bi nitrate | Rat* | 100 < | 2 < | 4 < | 0 < | 0 = |
| MATTHEWS** | 15 Table 2 | $^{206}$Bi citrate | Rat | 100 > | 1.4 > | 2.2 > | 1.0 = | — |
| VAN DEN BROEK | Present paper | $^{210}$Bi chloride | Rat | 100 | 54 | 22 | 17 | 21 |

* Control animals animals bearing tumours omitted
** Figures interpolated from those given for 19 and 48 hours
*Signs* < increasing = stationary > decreasing ∧ at a maximum

There are numerous data in the literature on the distribution of radioactive bismuth among organs but hardly anything about its accumulation in cells The former distribution mainly depends on the medium in which the bismuth is introduced, e g whether in aqueous solution (6 15 16 17, 19) in oil (6), bound to organic compounds such as carbonate lecithin (16, 17 18) or protein (15), or absorbed on coal particles (3, 15 22, 24) In connection with the present work, all results pertaining to the administration of bismuth other than in watery solution can therefore be left out of consideration As far as the author is aware the first autoradiographic data on the distribution after injection of a bismuth salt dissolved in water was given by LACASSAGNE & FOUCAULD (6) These authors, 4 to 10 days after the injection into rabbits found a very high accumulation in the renal cortex, a high concentration in the spleen, less in the liver, a scarcely perceptible amount in the bone marrow and practically none in lymph nodes, testes, thymus, adrenal and appendix KAHN (5) reported an accumulation of $^{210}$Bi in tumours but not elsewhere The findings of LACASSAGNE & FOUCAULD, although not presented on a quantitative basis, and determined at longer intervals after injection more or less agree with those of the present investigation

The only reports on the distribution after shorter time intervals are those by MATTHEWS (15) and PASSALACQUA (16, 17, 19), obtained by radiation

counting of $^{206}$Bi in entire organs and therefore not directly comparable with the results now given. As, however, the radiation countings are recorded as radioactivities per unit weight of kidney, liver, spleen, lung, and sometimes bone marrow, and as the track countings presented in this paper pertain to autoradiograms from uniformly thick sections of these same organs, some comparison of the relative radioactivities of these organs would seem possible. To this end, therefore, Table 3 was compiled. The results given by PASSALACQUA (16, 17, 19) for the 24 hour interval after administration of $^{206}$Bi nitrate in animals not bearing tumours are represented in relation to the radioactivity of the kidney (kidney = 100) in the table. The results by MATTHEWS for $^{206}$Bi citrate were also interpolated for 24 hours from her figures for 19 and 48 hours and likewise presented relative to kidney = 100. It is indicated in all cases whether the radioactivity seems to go up or down or to remain equal. The track countings from the present investigation, insofar as they were obtained from parts of organs (e. g. kidney tubuli, cortex, medulla), were converted to figures for the entire organs by due consideration of their composition as measured from serial sections, and the figures so obtained were again presented in relation to whole kidney = 100.

It is apparent from this table that there is a striking difference between the autoradiographic findings and all radiation counts (which among themselves are far from uniform). This must doubtless be ascribed to the fact that most of the bismuth that at the instant of fixation is still present in a soluble form will be washed out in the course of the histologic preparation for autoradiography. Most tracks in the autoradiograms will be derived from the $^{210}$Bi that is rendered insoluble either by the formation of larger aggregates or by binding to organic compounds. Although it has long been known that the isotope concentration and the method of injection may lead to varied degrees of aggregation (13), this does not seem to have been the case in any of the doses used in this investigation, because even in areas of the greatest track density no stars were evident. It must be concluded therefore that most of the autoradiographically detected $^{210}$Bi is bound to organic material, supposedly protein. The distribution of the tracks among all types of cells and tissues makes it seem likely that one day after injection the isotopes are still largely in a soluble form and freely pervading all tissues.

If it be assumed that the Bi ions on their course are somewhat randomly bound to organic matter, this would explain the presence of tracks over erythrocytes, connective tissue and bone, smooth muscle fibers of arteries and even over the histologically empty lumina of vessels and tubules. In such organs as accumulate the isotope(s), part of the amount incorporated by specific cells, such as the proximal tubuli cells of the kidney, may also have diffused out so that tracks are found over other cells of these organs as well.

The organs that specially accumulate the isotope for excretion are the kidney and, to a lesser extent, the liver, the bile of which was found to contain

much bismuth If indeed both organs collect Bi mainly in the soluble form, this would explain why these two organs register a much lower relative radioactivity in the autoradiograms than in total organ counting (Table 3)

A random binding of freely pervading Bi ions would also explain why a ratio of only 5 to 7 was found for a tenfold increase in dose The binding of the isotope to organic compounds would be less than proportional to its concentration, whereas a higher concentration would favour the loss by excretion

It is certainly not claimed that all discrepancies may thus be explained Due attention must be given to the fact that both the method of administration of the isotope (13) and its concentration (21) may influence the distribution in the body As to the present investigation, it has already been stated that the first possibility does not seem likely, whereas the second is rendered less probable by the regularity observed in Tables 1 and 2 The main question left open is to what extent these results have been influenced by the unknown quantity of $^{210}$Po formed out of the $^{210}$Bi If these isotopes had been accumulated by the various organs in a markedly different proportion, this would have resulted in a greater irregularity of the figures presented in the tables Their very regularity makes it seem fair to assume that the behaviour of Bi and Po in the animals was roughly similar as long as no data to the contrary are recorded

The distribution of polonium has been studied by LACASSAGNE and his co workers (7, 8, 9, 10, 12, 14) in what have become classics of autoradiography The investigations however, were made at much longer intervals after injection (4 to 10 days) and then the accumulation in the renal tubuli bile, and pulmonary dust cells (9) is much more marked, its accumulation in reticulum cells and macrophages even leading to extensive radiation damage (ref 10, 14) As with bismuth, distribution depends on the medium in which the isotope is administered, after its introduction in an aqueous form the accumulation in the kidney was found to be especially marked (ref 7) Indications on the distribution after 24 hours were reported only by GALLIMORE et coll (2) Their figures for percentage of dose per gram wet weight were kidney 2 8 (100), spleen 5 1 (183), liver 1 4 (50), or markedly different from those of the present investigation (Table 3) Their autoradiograms of tissues fixed after the same interval however, show many striking likenesses with those now described

Aside from a multitude of minor quantitative differences, the general picture for polonium, as for bismuth, is that 24 hours after injection the isotope is still far from being concentrated at its definitive locations The element is reported to be eliminated from the organism with an effective half life of approx 30 days (ref 4) and it is therefore not surprising that after one day only the first indication of the future accumulation is evident

The marked accumulation of the isotope(s) in the renal tubules observed in the present work has been found both for Bi and Po moreover it seems

to be the rule for a great number of elements administered to the organism in a soluble form This accumulation cannot therefore be considered to be specific for any isotopes

The present observations do not give the clear cut distinction in the spleen between red pulp on the one hand and white pulp, vessels, and connective tissue on the other as reported by LACASSAGNE et coll (10) and GALLIMORE et coll (2) for Po the slightly but systematically higher track density over the red pulp in the present work may however tentatively be considered to be a first indication of this distribution Likewise, the inconspicuous accumulation in the macrophages may be explained as the beginning of the accumulation observed so definitely by LACASSAGNE after 6 days

It appears therefore that such specific accumulation as has been found in the present work could almost equally as well be ascribed to the bismuth as to the polonium present in the injected material There is no indication as yet for any cellular specificity for Bi in soluble form It may be that such a specificity is overlapped by the Po present in that case a repetition of the experiment with a very freshly prepared solution of $^{210}$Bi may produce clearer results If however a specific accumulation of Bi does not develop until some days after the introduction of the isotope the accruing contamination by Po may well become prohibitive

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## SUMMARY

Rats were injected intravenously with doses of $^{210}BiCl_3$ and counts and distribution studies of the tracks of autoradiograms of various tissues were performed Track distribution in most cases conformed to the random distribution the only exceptions being a high accumulation in the proximal tubules of the kidney and a slight accumulation in the macrophages of the spleen

## ZUSAMMENFASSUNG

Ratten erhielten Einspritzungen von $^{210}BiCl_3$ worauf mit Hilfe von Autoradiogrammen von verschiedenen Geweben die Starke und die Verteilung der Strahlungsemission gemessen wurde Die Strahlung zeigte im allgemeinen eine gleichmassige Verteilung eine Anreicherung zeigte sich jedoch in den proximalen tubuli der Nieren und in den Makrophagen der Milz

## RÉSUMÉ

Après avoir injecte a des rats par voie intraveineuse du BiCl$_3$ l auteur a effectué des comptages et des études de distribution sur les autoradiographies de divers tissus Cette distribution est dans la plupart des cas conforme au hasard la seule exception etant une forte accumulation dans la partie proximale des tubes renaux et une faible accumulation dans les macrophages de la rate

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# COMPLICATIONS IN POSTOPERATIVE IRRADIATION OF MAMMARY CARCINOMA

## Observations in 585 patients treated at Radiumhemmet 1955—1960

by

FOLKE EDSMYR and RUNE WALSTAM

Different methods of irradiating parasternal lymphnode metastases have been investigated at Radiumhemmet One of the methods particularly developed for this purpose was described by EDSMYR & WALSTAM in 1959 and physical conditions for certain techniques were compared in a later paper (STROM VIKTERLOF & WALSTAM 1959) Postoperative irradiation of the parasternal region was performed in 585 patients from 1955 to 1960 on the basis of results from these investigations, from January 1958 until the end of 1960 120 of these patients were treated with 9 or 12 MeV electron beams while in the other 465 patients a short distance cobalt 60 beam technique was used

The treatments were started with relatively moderate doses since no experience had been gained either of early or of late reactions from the irradiated tissues The plan if circumstances allowed was to increase the doses gradually so that as high a dose as possible could be given to the lymphnode areas without causing intolerable complications functional disturbances or other radiation

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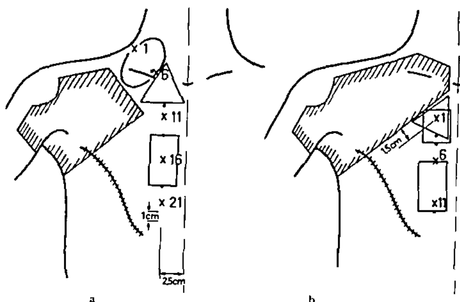



Fig 1 Scheme of irradiation with orthovoltage roentgen therapy and short distance cobalt 60 gamma beam therapy
a) Overlapping field including the parasternal and supraclavicular regions
fields 1 to 5 SSD 7 5 cm circular field diameter 6 cm
» 6 to 8 » = 7 5 cm triangular field side 5 cm
» 9 to 23 » = 6 cm field 3 5 × 6 cm
b) Overlapping field including only the parasternal region
Field 1 — triangular or partly covered field
Fields 2 to 14 – SSD = 6 cm Field 3 5 × 6 cm

reactions in surrounding organs (cf FLETCHER et coll 1962) The skin and lung reactions subjective symptoms and local complications in patients thus irradiated will now be dealt with The irradiation technique has successively undergone minor modifications suggested by the clinical observations The effect of irradiation on any parasternal and supraclavicular lymphnode metastasis that may have been present cannot be assessed from this series for it is relatively heterogeneous and the observation time has in most cases been too short

Preoperative roentgen irradiation (FSD 50 to 60 cm, HVL 0 8 to 1 0 mm Cu) was given in about two thirds of the patients and may be considered to have had some influence at least as far as skin reactions are concerned The irradiation was generally administered in a week by giving 3 × 350 r to frontal and dorsal fields that included the mamma and the axillary and supraclavicular regions

## Patients (465) treated by the short distance cobalt 60 technique

*Irradiation technique* A special technique was developed at Radiumhemmet (WALSTAM 1958) for irradiation of elongated superficial areas with short distance cobalt 60 units This comprises a great number (10 to 25) of over

lapping irradiation fields (SSD 6 to 10 cm) with some exceptions each field is irradiated once only, so that a homogeneous dose is obtained at the particular tissue depth For further data on this technique the reader is referred to earlier papers (EDSMYR & WALSTAM 1959 STROM VIKTERLOF & WALSTAM 1959)

Thirty eight patients were treated by a preliminary technique during the period December 1st, 1955 to August 31st 1956 a beam nozzle giving a field of 6 cm width at the skin at a source skin distance of 10 cm was used All the other patients were irradiated according to the schemes outlined in Fig 1 A specially designed beam nozzle giving a field of 3 5 cm width at the surface at 6 cm SSD, was then employed Two irradiations in different parts of the treatment area were administered daily in many of the patients for whom a great number of irradiation fields were utilized Only exceptionally was this procedure contraindicated, for instance by the patient s general condition The total duration of a treatment series was therefore 10 to 20 days

The dosage in short distance gamma beam therapy with radium or cobalt 60 because of measuring difficulties is generally expressed as the extrapolated skin dose This dose which is arrived at by extrapolating the depth dose curve obtained in tissue equivalent material to the depth 0 is often 5 to 10 per cent higher than the true dose maximum found at a tissue depth of 1 to 2 mm The surface doses now mentioned for instance the dose to each irradiation field (750 to 1 000 r) refer to the extrapolated skin dose The total skin dose used in the applied overlapping field technique is generally about six times the dose prescribed for each field

In the total group of 465 patients 213 were irradiated over both the supraclavicular and the parasternal areas whereas 252 patients received cobalt 60 irradiation over the parasternal region and orthovoltage roentgen therapy over the axillary and the supraclavicular regions

*Skin reactions* The skin reaction could be graded from the data of the records in 287 (62 %) of the patients irradiated by this technique according to the following schemes

I — moderate or slight reaction

II — *intense redness (no discharge)*

III — serous dermatitis (discharge)

The results from this grading are set out in Table 1

The skin reaction should increase with increasing dosage to the fields Such a tendency may be found in the preoperatively irradiated group but is hardly noticeable in the group of preoperatively non irradiated patients It will be seen from the table that middle dosages 850 to 900 r comprise 216 patients or 75 % of the total number The extreme groups are fairly small and cannot

**Table 1**

*Grade of skin reactions in patients treated by the short distance cobalt 60 technique*

| Dose per field r | Number of patients | Preoperative irradiation in 189 (66 %) cases | | | No preoperative irradiation in 98 (34 %) cases | | |
|---|---|---|---|---|---|---|---|
| | | Grade I | Grade II | Grade III | Grade I | Grade II | Grade III |
| 750 | 54 | 31 | 15 | 5 | 2 | 1 | 0 |
| 800 | 8 | 4 | 2 | 1 | 1 | — | — |
| 850 | 64 | 22 | 10 | 2 | 19 | 6 | 5 |
| 900 | 142 | 50 | 27 | 11 | 30 | 17 | 7 |
| 950 | 11 | 1 | 1 | 2 | 4 | 1 | 2 |
| 1 000 | 8 | 1 | 3 | 1 | 2 | 1 | — |
| Total | 287 | 109 | 58 | 22 | 58 | 26 | 14 |

**Table 2**

*Summary of results presented in table 1*

| Dose per field r | Number of patients | Preoperative irradiation | | | No preoperative irradiation | | |
|---|---|---|---|---|---|---|---|
| | | Grade I | Grades II + III | | Grade I | Grades II + III | |
| | | | Number | Percent | | Number | Percent |
| 750— 850 | 126 | 57 | 35 | 38 | 22 | 12 | 35 |
| 900—1 000 | 161 | 52 | 45 | 46 | 36 | 28 | 44 |
| Total | 287 | 109 | 80 | | 58 | 40 | |
| Average | | | | 42 | | | 41 |

therefore be expected to give significant deviations. If the patients are divided into two groups only, the distribution shown in Table 2 is obtained.

The small difference in the frequency of heavy skin reaction (grades II + III) between the groups of patients who received preoperative roentgen therapy (42 %) and those who had no such treatment (41 %) is surprising. It should be borne in mind, however, that the preoperative irradiation was administered in short series about 3 weeks before the postoperative irradiation was started. Its cumulative effect is therefore difficult to assess.

The patients' records in a great number of instances (178) contained no data on skin reactions. It may therefore be assumed that in all these the skin reaction was of grade I; on this assumption the incidence of marked skin reactions (II or III) should decrease from 40 % to 25 % of the total number of patients.

The most marked skin reaction was generally observed in regions with a thin

skin layer, particularly over the bones in the sternoclavicular area, as was to be expected Necrosis developed in the irradiated parasternal area after a dose of 900 and 1 000 r respectively per field in two patients The necrosis appeared in one patient 18 months and in the other a year after the termination of irra diation Both patients had received preoperative irradiation The first mentioned patient was 35 years old and had severe anaemia before, during and after the treatment, which might have influenced the postoperative course and the healing The other patient received a dose of 2 000 r to the first and the last treatment field, and it was in these regions that the maximum skin reaction and the necrosis occurred Healing is now complete and without complications after plastic surgery

Severe telangiectasis or superficial induration within the parasternal region occurred in the groups that had been given 850 r per field (5 patients) or higher doses The numbers of such patients were 4 in the group of 900 r per field one in the 950 r group and one in the 1 000 r group Three of these eleven patients had not been irradiated preoperatively

*Lung reactions* Thirty seven of the 38 patients treated according to the prelim inary technique at 10 cm SSD were examined roentgenographically for lung reactions immediately after the treatment and later No changes considered referable to the radiation treatment were observed in 27 Among the other 10 patients four have still, after 5 years, residual radiation reactions three have decreasing effects, and in three the changes have disappeared No subjective symptoms have been reported apart from those occurring immediately after the termination of treatment

Roentgenography of the lungs was performed in 164 of the other 427 patients, because of cough and increasing dyspnoea A radiation reaction was evident in 40 (24 %) of these patients The symptoms and signs disappeared after 2 to 3 months No difference was noted in the lung changes between the groups given 750 to 850 r per field and those receiving 900 to 1 000 r per field

*Subjective reactions* The symptoms and signs were slight excepting the skin and lung reactions mentioned earlier Induration was present however in the supraclavicular region in a small number of patients in each group it caused a reduction of the range of movement of the corresponding arm and in some patients fairly intense brachial pain No such complications were noted in the groups given 750 to 850 r per field but occurred in 2 patients in the group of 850 r per field in 13 of the group with 900 r per field and in 2 patients in the group that received 1 000 r per field The symptoms started about one year after the termination of the treatment

Dysphagia and other disturbances due to radiation effects in the oesophagus such as are reported to follow irradiation by other methods (FLETCHER et coll 1962) have not occurred in any of the patients in the present series

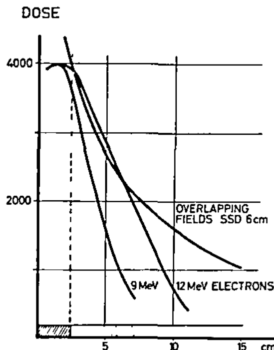



Fig 3 Approximative depth dose curves in the central part of the irradiated area (cf text)

the examination reveal evidence of radiation reactions No difference in the lung changes between the 9 MeV group and the 12 MeV group were observed

Among these 120 patients no important *subjective reactions* other than serous dermatitis in eleven (Table 3) and marked induration in the supraclavicular region in one patient were apparent

The *local complications* and the changes in the *blood picture* that occurred in this group of patients were not sufficiently severe to be mentioned in the case records or to necessitate any alterations in treatment planned for the series

## Discussion

The presence of metastases in the parasternal and supraclavicular lymphnode areas cannot as a rule be established in the individual case The treatment of these regions is based mainly on a probability estimation, in which for instance, the site of the primary tumour and the gross and microscopical appear f the surgical axillary specimen are important factors The irradiation is therefore planned to provide an adequate dose to those areas metastases are particularly likely to occur, without causing serious unreasonable distress to the patient

This investigation has shown that a dose of 850 r per field (extrapolated surface dose), when using short distance gamma beam technique or 4000 r, per field in electron beam irradiation with the treatment times stated, does not produce any noteworthy side effects. Preoperative roentgen therapy with about 1 000 r, 2 to 3 weeks before the postoperative radiation treatment does not seem to increase the skin reaction in any considerable degree.

The relative depth dose obtained with these treatment techniques in the middle parts of the treatment area and in the centre of the electron beam respectively is evident from Fig. 3. As pointed out earlier, a considerable spread of electrons is obtained in the lung cavities because of their lower density.

This material unfortunately permits no conclusions regarding the effects of the applied doses to any lymphnode metastases that may be present. The doses administered with these methods to the tissue volume concerned (cf. Fig. 3) seems, however, to be higher than the doses that because of the risk of skin and lung reactions can be given with *orthovoltage roentgen therapy*. Similar doses applied with a telegamma technique at larger source skin distances *have been reported* to cause serious pulmonary symptoms and dysphagia (FLETCHER 1962).

## SUMMARY

Two previously described methods for the irradiation of parasternal and supraclavicular lymphnode metastases have been used at Radiumhemmet, one based on the use of short distance gamma beam therapy, the other utilizing 9 or 12 MeV electrons from a betatron. A report is given of the irradiation conditions and the clinical observations in 585 patients treated with these methods during the period 1955—1960.

## ZUSAMMENFASSUNG

Zwei früher beschriebene Methoden mit Bestrahlung der parasternalen und supraclaviculären Lymphknotenmetastasen wurden am Radiumhemmet angewandt, eine Methode benutzte eine Gammastrahlung von kurzem Abstand, die andere Elektronen von 9 oder 12 MeV Energie. Der Bericht umfasst die Bestrahlungsfaktoren und die klinischen Einzelheiten von 585 Patienten, die mit den beiden Methoden in den Jahren 1955—1960 behandelt wurden.

## RÉSUMÉ

Deux méthodes précédemment décrites pour l'irradiation des métastases ganglionnaires lymphatiques parasternales et sus claviculaires dans le cancer du sein ont été utilisées au Radiumhemmet, l'une basée sur l'utilisation d'une gammathérapie à courte distance, l'autre utilisant les électrons de 9 ou de 12 MeV d'un bétatron. Les auteurs présentent les conditions d'irradiation et les observations cliniques de 585 malades traitées par ces méthodes de 1955 à 1960.

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# COMPUTER METHOD FOR TREATMENT PLANNING IN EXTERNAL RADIOTHERAPY

by

HANS HALLDÉN, INGER RAGNHULT and BENGT ROOS

Digital computers have proved to be very suitable for the calculation of dose distributions in radiotherapy with fixed or moving fields In the automatic dose calculation methods described by TSIEN (1955 1958) and STERLING, PERRY & BAHR (1961) polar co ordinate systems were used and the methods were restricted to beams intersecting in one point and to symmetrical beams SILER & LAUGHLIN (1962) schematically described a more generally applicable method Cartesian systems are used in the computer method described below it is not limited to symmetrical fields but is applicable to beams of any shape The method has been tried for different combinations of roentgen and cobalt 60 beams and has been in practical use for about a year it is now used mainly for the planning of cobalt treatments

*Isodose diagrams and codes* The isodose curves of the cobalt beams are measured in a water phantom with an ion chamber connected to an automatic isodose recorder (LARSSON LIDEN & STARFELT 1963) Source surface distances (SSD) of 60 and 80 cm are used and distributions with normal and oblique incidence, as well as with a number of wedge filters are measured

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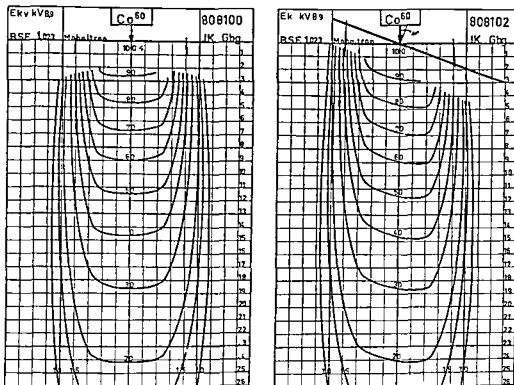



Fig 1 Isodose diagrams for 80 cm SSD Co field size 8 × 10 cm angles of incidence 0 and 20

The following code is used to identify the parameters

$$S\,a\,a\,b\,b\,u$$

where $S$ = SSD in decimeters $a\,a$ = field width in centimeters $b\,b$ = field length in centimeters $u$ = the angle between the central beam and the normal at the entrance point in deca degrees (For wedge filter diagrams we use $u = 5$)

Isodose curves for SSD = 80 cm field size 8 × 10 cm² and angles of 0 and 20 between the central beam and the normal are shown in Fig 1 The codes 808100 and 808102 are shown in the upper right corners of the diagrams

Before the isodose charts can be used for computing, they must be transferred to digital form The depth doses in per cent are read off at a number of points in a Cartesian system The values are obtained from the measured curves by interpolation, and are expressed in per cent (excluding decimals) The previously shown isodose diagrams transformed into digital lattices are shown in Fig 2

These field matrices are punched on paper tape, which is read into the

**808100**

Symm t YES

M x w dth 13 u t

Max l gth 26 u t

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 13 | 50 | 80 | 94 | 98 | 100 | | | | | | |
| 5 | 14 | 45 | 79 | 94 | 98 | 98 | | | | | | |
| 5 | 15 | 45 | 75 | 92 | 93 | 93 | | | | | | |
| 6 | 15 | 44 | 72 | 85 | 88 | 88 | | | | | | |
| 6 | 16 | 43 | 70 | 81 | 82 | 83 | | | | | | |
| 7 | 17 | 42 | 65 | 75 | 77 | 78 | | | | | | |
| 7 | 18 | 41 | 62 | 71 | 72 | 73 | | | | | | |
| 8 | 19 | 40 | 59 | 66 | 68 | 68 | | | | | | |
| 8 | 19 | 38 | 55 | 62 | 63 | 63 | | | | | | |
| 8 | 19 | 36 | 51 | 58 | 59 | 59 | | | | | | |
| 9 | 18 | 35 | 48 | 54 | 55 | 55 | | | | | | |
| 9 | 18 | 33 | 45 | 50 | 51 | 51 | | | | | | |
| 9 | 17 | 31 | 42 | 46 | 47 | 47 | | | | | | |
| 9 | 17 | 29 | 40 | 43 | 44 | 44 | | | | | | |
| 9 | 16 | 27 | 36 | 40 | 41 | 41 | | | | | | |
| 9 | 16 | 26 | 34 | 38 | 38 | 38 | | | | | | |
| 9 | 15 | 24 | 32 | 35 | 35 | 35 | | | | | | |
| 8 | 15 | 23 | 30 | 33 | 33 | 33 | | | | | | |
| 8 | 15 | 22 | 28 | 30 | 31 | 31 | | | | | | |
| 8 | 14 | 21 | 25 | 28 | 29 | 29 | | | | | | |
| 8 | 14 | 20 | 23 | 26 | 27 | 27 | | | | | | |
| 8 | 13 | 18 | 22 | 24 | 25 | 25 | | | | | | |
| 7 | 13 | 17 | 21 | 23 | 23 | 23 | | | | | | |
| 7 | 12 | 16 | 20 | 21 | 21 | 21 | | | | | | |
| 7 | 12 | 15 | 18 | 20 | 20 | 20 | | | | | | |
| 7 | 11 | 14 | 17 | 18 | 19 | 19 | | | | | | |

**808102**

Symm t NO

M x w dth 13 u it

M x l gth 26 u t

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 100 | 99 | 97 | 80 | 45 | 15 | 3 |
| | | | | | 99 | 98 | 96 | 93 | 80 | 45 | 15 | 3 |
| | | | 75 | 90 | 93 | 93 | 92 | 90 | 75 | 45 | 15 | 3 |
| 3 | 14 | 42 | 73 | 86 | 88 | 88 | 87 | 84 | 72 | 45 | 17 | 4 |
| 4 | 15 | 42 | 70 | 83 | 83 | 83 | 81 | 79 | 69 | 43 | 18 | 4 |
| 4 | 16 | 42 | 67 | 78 | 79 | 78 | 76 | 74 | 64 | 40 | 18 | 5 |
| 5 | 18 | 41 | 63 | 74 | 74 | 73 | 72 | 69 | 60 | 39 | 19 | 5 |
| 5 | 19 | 40 | 60 | 69 | 69 | 68 | 67 | 64 | 57 | 37 | 19 | 7 |
| 6 | 20 | 39 | 57 | 64 | 64 | 63 | 62 | 60 | 53 | 35 | 19 | 7 |
| 6 | 20 | 37 | 53 | 60 | 60 | 59 | 58 | 56 | 50 | 34 | 19 | 7 |
| 7 | 20 | 35 | 49 | 56 | 56 | 55 | 54 | 53 | 47 | 33 | 18 | 8 |
| 8 | 19 | 34 | 46 | 52 | 52 | 52 | 51 | 49 | 44 | 31 | 18 | 8 |
| 8 | 18 | 32 | 43 | 48 | 48 | 48 | 47 | 45 | 40 | 30 | 18 | 8 |
| 8 | 18 | 30 | 41 | 45 | 46 | 44 | 43 | 42 | 38 | 29 | 17 | 8 |
| 8 | 17 | 29 | 38 | 42 | 42 | 42 | 41 | 39 | 35 | 27 | 16 | 8 |
| 8 | 16 | 28 | 36 | 39 | 39 | 39 | 38 | 37 | 33 | 26 | 16 | 8 |
| 8 | 16 | 26 | 33 | 36 | 37 | 36 | 35 | 34 | 31 | 24 | 15 | 8 |
| 8 | 15 | 24 | 31 | 34 | 34 | 33 | 33 | 32 | 29 | 23 | 15 | 8 |
| 7 | 15 | 22 | 29 | 31 | 31 | 31 | 30 | 29 | 27 | 22 | 15 | 7 |
| 7 | 14 | 21 | 7 | 29 | 29 | 29 | 28 | 27 | 25 | 20 | 14 | 7 |
| 7 | 13 | 20 | 5 | 27 | 27 | 27 | 27 | 26 | 24 | 19 | 13 | 7 |
| 6 | 13 | 18 | 23 | 25 | 25 | 25 | 25 | 24 | 22 | 18 | 13 | 7 |
| 6 | 12 | 17 | 1 | 23 | 23 | 23 | 23 | 22 | 21 | 17 | 12 | 7 |
| 6 | 12 | 16 | 0 | 22 | 22 | 22 | 22 | 20 | 19 | 16 | 12 | 6 |
| 6 | 11 | 15 | 19 | 20 | 20 | 20 | 19 | 19 | 18 | 15 | 11 | 6 |
| 6 | 10 | 14 | 17 | 19 | 19 | 18 | 18 | 18 | 17 | 14 | 11 | 6 |

Fig 2 Field matri es obtained from the isodose diagrams in fig 1

computer where controls are made then the information is stored in a format more suitable for the dose planning program

A more rapid and accurate method of producing field matrices would be to let the ion chamber scan the radiation field and directly to record the doses at the different points of the lattice

*Co ordinates and angles* The contour of the body cross section is drawn on transparent paper The co ordinate axes and a contour with two treatment fields are shown in Fig 3 The $x$ and $y$ co ordinates of the entrance points of the beams are read off The beam direction angle $v$ is found when the positive $y$ axis is turned clockwise until it coincides with the direction of the central beam The

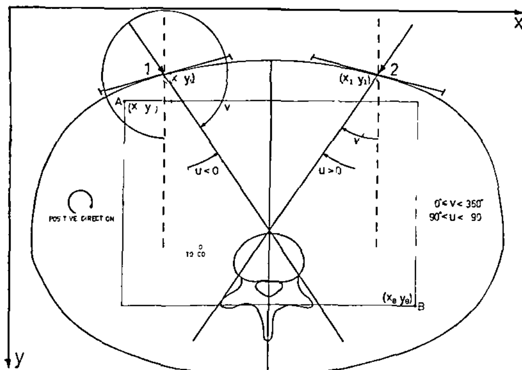



Fig 3 Schematic diagram showing co-ordinates and angles

**Table 1**

*Dose planning Nr 33/621113*

| Field | Sym pos neg | x | y | k | i |
|---|---|---|---|---|---|
| 808102 | neg | 7 4 | 0 2 | 1 00 | 330 |
| 808100 | sym | 26 2 | 2 8 | 1 00 | 50 |
| 808102 | neg | 22 1 | 19 7 | 1 00 | 140 |
| 808102 | pos | 0 8 | 18 1 | 1 00 | 240 |
| | | | | | |
| | | | | | |
| | | | | | |

A ☐ B

| | x | y |
|---|---|---|
| A | 0 | 0 |
| B | 29 | 21 |

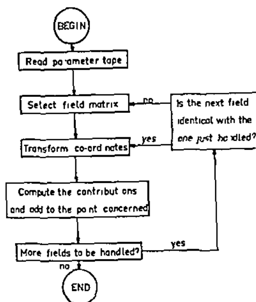



Fig 4 Block diagram showing the computer program

boundaries for $v$ are $0 \leq v < 360°$ The angle of incidence $u$ is defined as the angle between the central beam and the normal to the contour at the entrance point and varies between the limits $-90$ and $+90$ It is defined as positive if the normal mentioned can be brought to coincide with the central beam by a positive (clockwise) turn In Fig 3 $u$ is negative for field 1 and positive for field 2

The area within which the computer has to add the contributions from the fields is chosen as a rectangle that well covers the tumour region as well as other regions having importance for the treatment The maximum size of this rectangle is 48 cm along the $x$ axis and 32 cm along the $y$ axis The co ordinates for the two corners $A$ and $B$ defining the rectangle and all the radiation parameters mentioned above are recorded on an order form (Table 1)

## The computer program and examples

The program is described by the block diagram (Fig 4) so we will just make a few remarks

The data on the order form is transferred to paper tape and the result is given on paper tape

The computer work follows a program with about 1 500 instructions

The wanted contribution from one field to a point $(x\ y)$ in the area is determined as follows

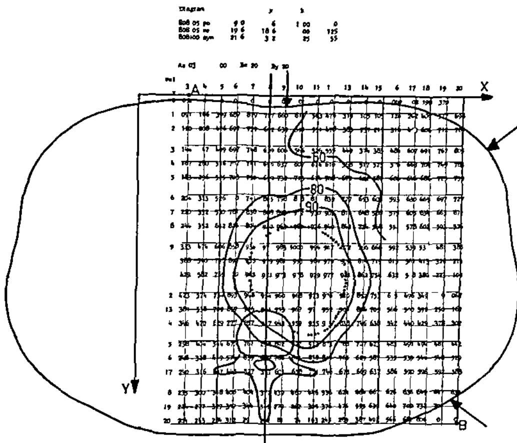



Fig. 5. The figure shows the isodose lines being drawn on the cross-sectional diagram which is super-imposed on the result form. The completed diagram is shown in fig. 7.

Let $F(x, y)$ be the dose at the point $(x, y)$; then if $F(x, y) = A\,x + B\,y + C\,xy + D$ we have to find the four constants $A$, $B$, $C$ and $D$. First we transform the co-ordinates of the point to the co-ordinate system of the field, and there it usually becomes surrounded by four points, which we give the co-ordinates $(0, 0)$, $(1, 0)$, $(0, 1)$ and $(1, 1)$ with the doses $F(0, 0)$, $F(1, 0)$, $F(0, 1)$, and $F(1, 1)$.

Then
$$F(0, 0) = D$$
$$F(1, 0) = A + D$$
$$F(0, 1) = B + D$$
$$F(1, 1) = A + B + C + D$$

and
$$D = F(0, 0)$$
$$A = F(1, 0) - F(0, 0)$$
$$B = F(0, 1) - F(0, 0)$$
$$C = F(1, 1) - F(1, 0) - F(0, 1) + F(0, 0)$$

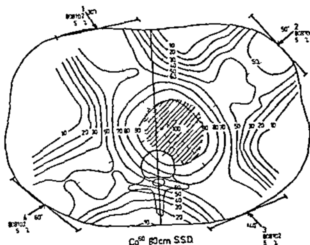



Fig 6 Distribution resulting from four fields

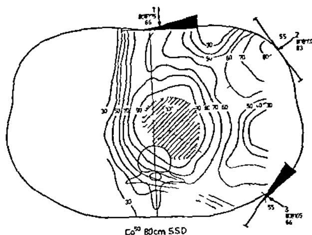



Fig 7 Dose distribution obtained from two wedge fields and one normal incidence field

and these constants multiplied with the decimal fractions of the transformed co-ordinates according to the formula give us the dose contribution from this one field to this special point

The result paper tape is written out on a flexowriter Over the result form we put a film with 1 cm squares and over this the transparent paper with the body cross section On this paper the isodose curves are easily drawn (Fig 5) This last moment can be omitted if the computer is connected to a plotter

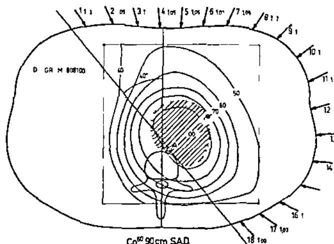



Fig 8 Dose distribution obtained from 18 fixed fields simulating moving field irradiation with 180 oscillation angle

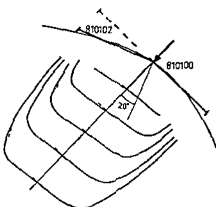
The usefulness of the method is illustrated by three examples which show some different proposals for treating a tumour

*Example 1* is calculated with the parameters of the Table, and the percental dose distribution obtained, is shown in Fig 6

*Example 2* illustrates how with three fields we get a somewhat different distribution (Fig 7) (Fig 5 shows how the isodose curves are drawn on the transparent paper )

*Example 3* is an arc therapy calculation with an oscillation angle of 180 The positions of the oscillation axis and of the fields are marked in Fig 8 The computing is done with 18 fixed fields with 10° angular intervals, size 8 × 10 cm² source axis distance (SAD) = 90 cm Here we have to consider that the SSD is a variable The variation in SSD has a negligible influence on the isodose distribution and on the percental depth dose, but the dose rate at the different entrance points has a considerable variation, and hence the contribution from each field has to be multiplied by a factor This factor is automatically computed by means of the inverse square law

*Checking, errors, and corrections* The manual calculation of the dose at a few essential points is a precaution that always should be taken On a comparison of these check values with the computer result it is found that the computed values are often a few per cents below those calculated by hand The greatest errors appear at the field borders and are due to the fact that the computer fills




$Co^{60}$ 80cm SSD

Fig 9 Mixed isodose diagram

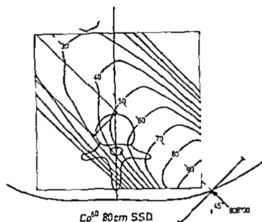



Fig 10 Distribution obtained when the correction factor 0 90 is applied to points in the rectangle behind the vertebra

the empty columns of the field matrix with zeros, so that the interpolation formula gives an underestimated dose at a point surrounded by one or more field points with the value zero These marginal errors which generally are of secondary importance will be smaller if we increase the width of the field matrices but as this would increase the work to read off the diagrams we have to balance the errors to the extra work Near the central axis the errors usually lie between 0 and 2 % which we consider a sufficient accuracy

When a field is applied obliquely to the body surface we use the proper measured diagram There is, however sometimes a need for diagrams which on one side of the central beam are close to normal incidence and on the other side to oblique incidence (Fig 9) Mixed diagrams of this kind are easily produced by the computer

When irradiating tumours in the thorax region we can compensate for the increased transmission in the lung tissue either by moving the entrance points of the fields closer to the tumour or by introducing tissue factors

For the decreased transmission in bone tissue we can compensate in a similar manner In those cases where only a part of the beam is penetrating bone we can use the tissue factor within a limited area of the field matrix The isodoses when the field points within the rectangle are multiplied by the factor 0 90 are shown in Fig 10

*Series of standard dose diagrams* The computer method described above is well suited for precalculation of standard multiple and moving field dose distributions (DAHL & VIKTERLOF 1960 PFALZNER 1962) Calculations on a series of fixed field distributions of circular cross sections are carried on

## SUMMARY

A method of automatic computation of dose distributions in multifield and moving field therapy is described. The isodose diagrams have been transferred to numerical lattices in a Cartesian system and punched on paper tape. The treatment area has been drawn in another Cartesian system in which the dose contributions from the different fields are added at a number of points. The calculation was carried out on a digital computer. The method is illustrated by examples and corrections for different types of tissue are discussed.

## ZUSAMMENFASSUNG

Eine Methode zur automatischen Berechnung der Dosisverteilung bei Kreuzfeuer oder Bewegungsbestrahlung wird angegeben. Die Isodosenkurven wurden in numerische Matrizen eines kartesischen Koordinatsystems überführt und auf Papierstreifen gestanzt. Das Bestrahlungsgebiet wurde in ein anderes kartesisches System eingezeichnet, in dem die Dosisbeiträge der verschiedenen Felder in einer Anzahl Punkte addiert wurden. Alle Berechnungen wurden mit Hilfe eines digitalen Komputers ausgeführt. Die Methode wird an Beispielen illustriert und Korrekturen für verschiedene Gewebsarten werden besprochen.

## RÉSUMÉ

Description d'une méthode de calcul automatique de la distribution de dose dans le traitement par champs multiples et par cyclothérapie. Les courbes isodoses sont reproduites en coordonnees cartésiennes puis transcrites sur bande perforée. La région à traiter est représentee sur un graphique ou les distributions de dose provenant des differents champs sont additionnées en un certain nombre de points. Le calcul est effectué par une calculatrice digitale. Les auteurs donnent des exemples de cette méthode et étudient les facteurs de correction pour les différents tissus.


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# GIANT HEMANGIOMA AND THROMBOCYTOPENIA IN A NEWBORN INFANT TREATED BY IRRADIATION THERAPY

Case report

by

U FURUHJELM, P MAKELA and A VOUTILAINEN

The simultaneous occurrence of hemangiomas and thrombocytopenic purpura is unusual The first report of a case of this now generally accepted clinical syndrome was published by KASABACH & MERRITT in 1940 and more than 40 cases have since then been quoted in the literature HILL & LONGINO (1962) described two cases of their own and reviewed earlier case reports

The size of the tumour and the severe bleeding tendency in these patients frequently pose considerable therapeutical problems The present case concerns a newborn baby with a rapidly growing hemangioma and severe thrombocytopenia in which good clinical improvement was obtained by roentgen irradiation therapy

## Case report

A boy born by spontaneous delivery after a full term uncomplicated pregnancy weight at birth 4 450 g general condition good and skin colour normal A large tumour which appeared to be a hemangioma was evident in the left thigh no petechiae or other signs of bleeding were

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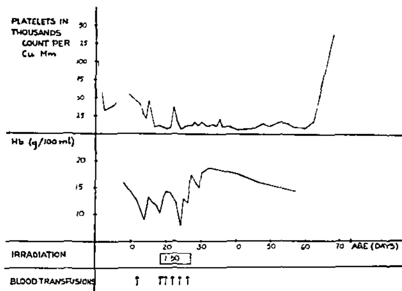



Fig 1 Hemoglobin concentration and platelet count while in hospital The days on which transfusion and roentgen therapy were given are indicated

apparent When the child was two days old the hemoglobin value was 16 7 g/100 ml and the thrombocyte count 99 000/mm on the fourth day the thrombocyte count had dropped to 33 000/mm and the child was transferred to the Childrens Clinic

On admission the child s condition was still good and no signs of bleeding were evident The liver extended 3 cm below the costal margin and the spleen was not palpable An elevated hemangiomatous mass purple in colour firm and immovable and 1 5 cm in size was present over the right thigh almost the whole of which was involved except for a small area posteriorly The adjacent skin was not sharply demarcated from the mass The leg appeared to be otherwise normal The hemoglobin concentration was 15 5 g/100 ml and the white cell count 14 300/mm the thrombocyte count was 59 000/mm³ *The variations in hemoglobin concentration* and platelet counts are depicted in Fig 1 The prothrombin and bleeding times were normal Tibial bone marrow aspiration disclosed a cellular marrow with slight myeloid hyperplasia and normal erythropoiesis megakaryocytes were present and seemed to be increased in number though they were normal in form and possessed a granular cytoplasm *Biopsy* suggested a capillary hemangioma with considerable endothelial proliferation

*Roentgen examination* revealed only soft tissue swelling of the thigh the bone appeared to be intact The tumour increased progressively in size during the following two weeks to form a circular mass that extended distally below the knee and proximally to the gluteal region (Fig 2) There was marked edema of the leg

From the age of two weeks the child bled continuously from numerous small ulcerations on the surface of the tumour at the same time he gained as much as 100 g a day in weight though this may be attributed in part to bleeding into the mass The blood loss was considerable and sufficient blood volume was maintained by frequent transfusions of fresh blood 800 ml in all were given (Fig 1)

*Irradiation therapy* was started when *the child was 18 days old The tumour* was cross fired through two fields each measuring 8 × 10 cm factors 180 kV, filter 0 5 mm Cu FOD 40 cm and HVL 1 1 mm Cu A total of 1 150 r to each field was given on consecutive days in single



Fig 2 Appearances of tumour prior to treatment



Fig 3 The th gh at the control examinat on

doses of 300 r with one of 250 r A lead rubber sheet 3 mm thick was used to protect the gonads and epiphyseal lines the secondary radiation caused by each single treatment (300 r) was measured as being 2 3 r to the gonads and 2 0 r to the nearest epiphyseal line

The tumour felt much harder after a few days and there were signs of inflammation which included local elevation of temperature and maceration of the skin The growth of the tumour was clearly inhibited and in spite of persistently low platelet counts the bleeding subsided towards the end of the treatment period Clear improvement in the baby s general condition which had been rather poor during the period of severe bleeding was apparent at this stage On the other hand there was no marked change in the size of the tumour and it was not until 38 days after the treatment was completed that the platelet count rose dramatically and then remained normal (Fig 1) The skin lesions al o gradually healed and the child was discharged after 67 days in hospital

At control examination 3 months later when the baby was 5 months old his general condition seemed to be satisfactory The tumour had almost disappeared leaving a fibrotic scar formation 5 × 10 cm in size and firm to the touch There was no difference in the circumference of the thighs (Fig 3) The peripheral blood picture was normal as was the bleeding time The thrombocyte count was 265 000/mm The growth of the femora appeared roentgenographically to have been equal

## Discussion

Thrombocytopenia and a tendency to bleeding in connection with a hemangioma is rare immediately after birth Hemorrhage in this period constituted a problem in only 5 of reported cases (Hill & Longino 1962) The remaining cases reported were mostly in infants and children with a few in the older age

groups The thrombocytopenia usually appears during a period of rapid growth of the tumour, though cases with multiple small hemangiomas have also been described (GILON et coll 1959, FISCHLER 1960) Diagnostic difficulties may arise when the hemangioma is situated subcutaneously or internally, e g in the intestine (JAMES & TUTTLE 1961, HILL & LONGINO 1962, BACKMAN & PARKKULAINEN 1958) Because of the tendency to severe bleeding biopsy has been performed only in a limited number of cases and has revealed either a simple benign hemangioma, a capillary hemangioma or a hemangioendothelioma Reports of bone marrow studies have not, however, recorded significant abnormalities except for immature megakaryocytes and a decreased or an increased number of these cells

Several theories have been put forward to explain the process by which the thrombocytopenia is produced (SILVER et coll 1948, SOUTHARD et coll 1951, GOOD et coll 1955, GILON et coll 1959, BLIX & AAS 1961)

Various therapeutic measures, including supportive treatment, have been used in this syndrome Steroids have occasionally been administered but without obvious beneficial effect on the thrombocytopenia (HILL & LONGINO 1962) they may, however, have prevented bleeding by raising the capillary resistance Splenectomy has been performed in 8 cases with resultant improvement in the thrombocytopenia in one case (MEEKS et coll 1955) Infusions of platelet concentrations restore the bleeding time to normal only for a very limited period but are of the greatest value before and during operative procedures

The choice of treatment appears to lie between radical removal of the tumour and irradiation therapy If the hemangioma is successfully excised there is a prompt rise in the platelet counts (INGLEFIELD et coll 1961, HILL & LONGINO 1962) Operation is, however, ruled out in many cases because of technical difficulties or because of the great risk of excessive bleeding Roentgen treatment results in cessation of the growth of the tumour and in its gradual shrinkage The rise of the platelet count is slower than after surgery and occurs from one to several weeks after the treatment (SOUTHARD et coll 1951, JAMES & TUTTLE 1961, SUTHERLAND & CLARK 1962) The period was about 5 weeks in the present case, on the other hand the bleeding from the tumour ceased much earlier when the treatment was completed apparently as a result of the irradiation

The irradiation dose was the usual one for hemangiomas and other benign tumours The depth of the tumour was estimated to be approximately 3 cm, and a HVL of 1 1 mm Cu was used The expected results were achieved the growth of the tumour was checked, the thrombocyte count became normal and there were no signs of epiphyseal damage evident at the follow up examination

Disapproval of irradiation therapy is based upon the fear that secondary radiation may damage the gonads and epiphyseal lines The total gonad dose in the present case was 18 r and 104 mr, and the dose to the femoral epiphyses

15 r and 320 mr respectively The therapy would appear to have caused no somatic damage but it is of course too early to evaluate possible genetic disturbances

The writers believe that irradiation is indicated for cases with massive hemorrhages where radical treatment is impossible A combination of irradiation and surgery might be advantageous, the acute stage could be controlled by radiation therapy and the tumour excised later (HILL & LONGINO 1962)

## SUMMARY

A case of a newborn boy with a rapidly growing giant hemangioma and thrombocytopenia treated with roentgen irradiation is reported The treatment resulted in a decrease in the size of the tumour and a rise in the platelet count Some of the therapeutical aspects are briefly discussed

## ZUSAMMENFASSUNG

Ein Fall von einem neugeborenen Jungen mit einem rasch wachsenden Riesenhaemangiom und mit einer Thrombocytopenie behandelt mit Rontgenstrahlen wird beschrieben Die Behandlung fuhrte zu einer Verkleinerung des Tumors und einer Besserung in den Thrombocyten Einige Punkte der Therapie werden erortert

## RÉSUMÉ

Les auteurs présentent le cas d un garçon nouveau né atteint d un hémangiome géant croissant rapidement et de thrombocytopénie qui fut traité par roentgenthérapie Le traitement amena une diminution du volume de la tumeur et une augmentation du nombre des plaquettes Les auteurs discutent brièvement certains problèmes concernant le traitement

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FROM THE CANCER RESEARCH LABORATORIES, MEHARRY MEDICAL COLLEGE, NASHVILLE, TENNESSEE, U S A

# LONG TERM STUDIES IN DOGS RECEIVING SINGLE MASSIVE INJECTIONS OF RADIOACTIVE IRON DURING GROWTH

by

P F HAHN and E L CAROTHERS

Concern as to the long term effect of internal exposure to radioactive isotopes is not new Interest originally centered not only on the pseudo-medical use of water containing radon many years ago but also on those individuals who were exposed by their own carelessness, ignorance or otherwise to radium in the course of dial painting during World War I Such individuals have been studied extensively by many workers The increase in potential exposure to long lived and therefore possibly carcinogenic and genetically important artificially produced radioactive isotopes and fission products has resulted in the extensive re investigation of the effects of exposures to such agents in laboratory animals and also in humans A great amount of such work has for many years been carried on at Argonne National Laboratory, and its predecessor the Metallurgical Laboratory of the University of Chicago in connection with the study of strontium barium cesium yttrium and plutonium in experimental animals Similarly studies on the concentration and long term effect of plutonium polonium and radium have been conducted at the University of California at

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Berkeley, and at the University of Rochester More recently the effects of relatively long lived $^{14}C$, *tritium and uranium isotopes have been studied* at various laboratories Strontium 90 is of course one of the fission products which is currently being widely investigated as to its carcinogenic potentialities at various levels of introduction by different routes

We have always looked upon any nuclide with a half life of ten days or more, especially one which has a tendency to concentrate in specific tissues, with a degree of suspicion as concerns carcinogenicity when introduced in quantities which are currently thought to be dangerous Our concepts of maximal permissible doses are necessarily undergoing re evaluation with increasing experience but in general one might say that American usage of isotopes has been on the conservative side

In 1941 we first described the use of the $^{59}Fe$ isotope for tagging the hemo globin of red blood cells in donor dogs for the purpose of determining the circulating mass of erythrocytes of recipients (6) (7) The chief advantage of this method over that used by HAHN and HEVESY, and subsequently by NYLIN using $^{32}P$ rested in the fact that once established in the hemoglobin molecule the iron was firmly bound and remained within the red cell throughout its life span In using iron as a tag there was no constant exchange in the body of the label with that of other compounds containing iron (4) The chief dis advantage in the use of the $^{59}Fe$ isotope by the method described lay in the technical problem of building up donors and also in the complicated methods required for measurement of the iron radioactivity in 1941

World War II brought to the front two major problems in which the iron tagged red cells proved to be of considerable value, namely in the investigation of shock and in the study of blood preservation After considerable amount of experience under battle conditions, it was finally recognized by the Armed Forces that where considerable blood loss had occurred the infusion of whole blood rather than plasma was required to combat shock Therefore several major programs were established to determine what materials would constitute the best preservatives for whole blood and/or red cells Studies of this sort were set up under the leadership of various investigators and these individuals also used the donor tagging technique in their human studies Our own efforts (3) (9) and that of many others were confined largely to the study of the red cell and total blood volumes in malaria, shock, polycythemia and other conditions of interest

In present day tracer studies for diagnostic purposes every effort is made to reduce the amount of total radioactivity introduced into a relatively normal individual With improved instrumentation the use of smaller and smaller quantities of isotopes is feasible However, during World War II the instrumen tation methods were far from ideal necessitating the employment of larger amounts of radioactivity This was particularly true in the case of volunteer donors who were employed for the studies mentioned above

It has been shown following the administration of iron to growing animals that nearly complete utilization of this material is accomplished in formation of hemoglobin in the peripheral circulation (5) and that once established the iron is re utilized repeatedly in red cell hemoglobin construction (1) The $^{59}$Fe activity is dissipated in six half lives which one would expect to span two life cycles of the red cells Therefore these isotopes with their long half lives ($^{59}$Fe = 47 days and $^{55}$Fe = 2 9 years) by their nature carry with them a low level of constant irradiation over long periods of time Fortunately the spectra of these isotopes are such that little radiation beyond the vascular system is anticipated With the $^{59}$Fe isotope the beta component is quite weak and in the case of the $^{55}$Fe the K capture electron results in the emission of a very soft roentgen beam Nevertheless it seemed advisable to determine whether or not any recognizable deleterious effects might be noted in long term experiments in animals in which the circulating titre of radioactivity was increased manyfold over that used in the past

It was thus decided to study whether in the dog $^{59}$Fe in quantities of many hundred times those employed in the war time studies could be tolerated without embarrassment of the hematopoietic system or ultimate development of neoplastic conditions For this reason in October 1950 and again in June 1952, a litter of hounds, in each year, was injected with the maximal quantities of radioactivity available at those times in the form of radioactive iron

## Methods

$^{59}$Fe is usually made by either a d p reaction in the cyclotron or by an n y reaction in the pile Its production efficiency is low primarily due to the small natural abundance of the parent $^{58}$Fe isotope this being only about 0 25 per cent normally Specific activities necessary for the use of large total radio activities would thus not be normally attainable within the toxic limits of the amount of iron which would have to be administered Therefore for our purpose $^{58}$Fe was enriched by electromagnetic separation procedures at Oak Ridge (We are indebted to Dr P C Aebersold who made the arrangements for electro magnetic concentration and subsequent special bombardment of the iron used in these studies ) The resultant 80 per cent abundant isotope was then subjected for several months to the thermal neutron flux of high intensity at Hanford Washington The resultant material contained approximately 1 millicurie $^{59}$Fe activity per milligram of iron Thus in 1950 and 1952 the total and specific activities were very considerably greater than those previously produced The material was prepared in colloidal form and administered by vein to the dogs in order to ensure maximum utilization

The dogs in the first experiment in 1950 were litter mates and were marked 50—1, 50—2 50—3 and 50—5 They were nearly pure bred blue tick hounds They were approximately two months of age when acquired with their mother

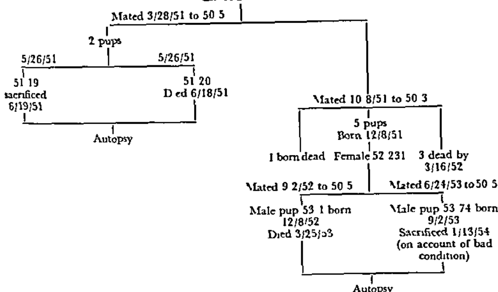
**Table**

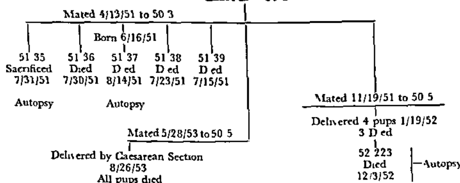
*Annual summary of hematologic examinations and growth*

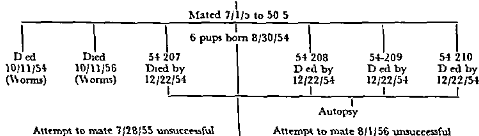
| Dog | Date | RBC | Hct | WBC | Segs | Lymph | Staffs | Juv | Eos | Mono | Wgt Lbs |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 50—1 (treated) | 10- 5-50 | 7 64 | 44 5 | 16 000 | 51 | 13 | 21 | 3 | 2 | 10 | 29 0 |
| litter 1 ♀ | 10- 5 50 | 1 mC of ⁵⁹Fe injected I V | | | | | | | | | |
| | 9-22-51 | 5 12 | 49 0 | 13 850 | 42 | 38 | 6 | | 12 | 2 | 33 5 |
| | 9-25-52 | 7 67 | 54 0 | 12 100 | 42 | 35 | 13 | | 8 | 2 | 38 0 |
| | 9-23-53 | 4 74 | 48 0 | 13 450 | 57 | 34 | 6 | | 1 | 2 | 41 1 |
| | 9-29-54 | 7 47 | 49 0 | 13 150 | 65 | 32 | | | 3 | | 45 0 |
| | 10- 1-55 | 6 42 | 52 0 | 8 950 | 69 | 14 | 15 | | | 2 | 46 2 |
| | 9 29-56 | 5 41 | 51 0 | 12 050 | 69 | 25 | 5 | | 1 | | 49 0 |
| | 11-29-56 | Sacrificed and autopsied | | | | | | | | | 48 5 |
| 50—5 (control) | 10- 5-50 | 8 26 | 47 0 | 11 600 | 46 | 21 | 18 | 2 | 1 | 12 | 29 0 |
| litter I ♂ | 9-22-51 | 5 41 | 50 0 | 10 425 | 41 | 30 | 11 | | 16 | 2 | 37 1 |
| | 9-25-52 | 7 95 | 52 0 | 13 450 | 58 | 20 | 11 | | 8 | 3 | 39 7 |
| | 9-23-53 | 7 72 | 49 0 | 14 875 | 69 | 22 | 1 | | 8 | | 8 8 |
| | 9-29-54 | 8 09 | 55 0 | 9 550 | 67 | 29 | | | 4 | | 39 5 |
| | 10- 1-55 | 7.23 | 58 0 | 6 500 | 60 | 19 | 16 | | 3 | 2 | 39 9 |
| | 9-29-56 | 6 10 | 56 0 | 9 025 | 53 | 33 | 11 | | 1 | 2 | 41 0 |
| | 11-29-56 | Sacrificed and autopsied | | | | | | | | | 41 0 |
| 52—218 (control) litter II ♀ | 6-27-52 | 5 09 | 39 0 | 18 050 | 68 | 21 | 4 | | 5 | 2 | 28 0 |
| | 6-24-53 | 4.38 | 50 0 | 13 875 | 71 | 25 | 2 | | 2 | | 35 5 |
| | 6-30-54 | 6 95 | 51 0 | 9 325 | 77 | 23 | | | | | 35 0 |
| | 6-28-55 | 7 92 | 59 0 | 6 975 | 46 | 21 | 11 | | 16 | 6 | 34 0 |
| | 6-27-56 | 7 51 | 53 0 | 16 725 | 69 | 20 | 5 | | | 6 | 33 7 |
| | 9-29-56 | 6 12 | 56 0 | 6 725 | 66 | 27 | 2 | | 3 | 2 | 34 0 |
| | 11-29-56 | Sacrificed and autopsied | | | | | | | | | 34 8 |
| 52—221 (treated) litter II ♂ | 6-27-52 | 6.24 | 40 0 | 20 000 | 61 | 23 | 4 | | 5 | 7 | 16 6 |
| | 6-28-52 | 3 3 mC of Fe injected I V | | | | | | | | | |
| | 6-24-53 | 7.57 | 58 0 | 14 225 | 67 | 29 | 3 | | 1 | | 38 5 |
| | 6-30-54 | 5 70 | 48 0 | 12 550 | 76 | 24 | | | | | 38 4 |
| | 6-28-55 | 7.23 | 55 0 | 12 625 | 79 | 6 | 10 | | 3 | 2 | 41 3 |
| | 6-27-56 | 6 90 | 56 0 | 11 700 | 71 | 13 | 3 | | 4 | 9 | 45 0 |
| | 9-29-56 | 6 17 | 52 0 | 10 725 | 51 | 29 | 9 | | 8 | 3 | 43 2 |
| | 11-29-56 | Sacrificed and autopsied | | | | | | | | | 44 2 |

(50—4) on 23rd of June 1950 At that time they were vaccinated against distemper and dewormed The first three dogs of this litter were injected at six months of age with 1 mC each of ⁵⁹Fe during an active growing period without previous phlebotomy A control litter mate, 50—5, maintained as the others on a commercial diet of 'purina dog chow', was not injected with radioactive material Before injection erythrocyte count hematocrit and leucocyte count, including differential counts, were found to be within normal limits

## GENEOLOGY OF INTERBRED DOGS



All the puppies had shown normal development and had gained weight during a period of four months between acquisition and injection

Hematologic studies were carried out at monthly intervals for the next six years by five individual student fellows working approximately one year each (The hematologic examinations were performed by Marvin Jackson, Frank Staggers, James Utley, William Andrews and Douglas Foster) Data are summarized in the Table These consisted of hematocrit values, erythrocyte and leucocyte counts, differential counts and sedimentation rates The weights, and signs of clinical well being of these animals, were also recorded regularly for six years On July 28, 1953, a test study of thick dehemoglobinized smears was negative for microfilaria on all dogs of both litters At the end of five years, bone marrow (rib) biopsies were obtained, and at the end of the sixth year these animals were sacrificed in November 1956 for gross and histologic analyses by the use of intravenous pentobarbital sodium in excess The dogs 50—2 and 50—3 had for various reasons died before this date

After having become adults (approximately one year of age) these animals were interbred whenever possible Dog 50—1, which had received $^{59}$Fe, was mated a year after injection to a male litter mate 50—3, also injected with iron, and as a result five pups were born on December 8, 1951 Of these, one was born dead and three of the others were dead within three months time However, one female, 52—231, survived throughout the ensuing five year period She was sacrificed along with all the other living animals in November 1956 In the meantime she was mated on two occasions with the control litter mate 50—5 of the original group (see geneology chart I) and as a result of the first pregnancy had one male pup which lived three and a half months, dying, as far as could be determined, of pneumonia The second pregnancy of 52—231 also resulted in the delivery of a single male pup born on September 2nd, 1953 and this animal was sacrificed four months after birth in poor condition, and autopsy again revealed pneumonia as the cause of death It is to be noted that in none of the second and third generation inbred animals were there any notable changes either grossly or histologically No visceral changes were encountered or hematopoietic alterations suggestive of any deleterious effect due to the burden of radioisotope in the predecessors It is apparent that our animal house was unsuitable for breeding and maintenance of puppies Therefore, there was a limited number of surviving of first and second generation animals to be studied

The dogs 52—218 52—219 52—220 52—221, 52—222 (control 52—218) in the second experiment were also litter mate hounds of about half the weight of the earlier group, and were injected with $^{59}$Fe on June 28, 1952, as follows 52—218 (control none), 52—219 received 0 74 mC, 52—220 received 1 5 mC, 52—221 received 3 3 mC, and 52—222 received 2 6 mC They were put on the same study regime as the litter *injected* with radioactive iron in 1950 and when injected were about six months old, the same age as the first litter The

rib biopsies on these latter dogs were done two and a half years after the injection of radioactive iron Attempts to raise puppies of 52—222 the only female in this litter, were not successful

The second litter was also sacrificed in November 1956 by pentobarbital sodium four and a half years after the iron injections One dog from this litter, 52—220 had died two months after injection No cause of death was found at autopsy

## Observations

When the females became adult (one year or more in age) they were interbred with treated male 50—3, or control male 50—5, on several occasions in an attempt to study the second or third generation anomalies that might develop, 50—1 as an example was mated on March 28 1951, to dog 50—5 About 7 weeks later her weight was 36 4 lbs and five days later she delivered two live pups, two days after delivery her weight was 30 0 lbs Her weight on October 8, 1951 was 36 0 lbs at which time she was mated with 50—3 on December 8 1951 five pups were born of which one was dead at delivery Three days later the weight was 34 7 lbs At this time, due to an anemia suspected to be on a basis of repeated pregnancy, injections of 100 mg equivalent of elemental iron in the form of 'Feojectin' (supplied through the courtesy of Smith Kline and French Co) were made on each of two days Two weeks later 80 mg of iron equivalent in the form of ferrous gluconate (kindly supplied by Dr Georg Cronheim of the Massengill Co) were administered on each of two successive days Litter mates including the control and the treated male received the same treatment Of the pups born in December 1951 all had died by March 16, 1952 except one female The surviving animal was retired to the country to insure survival and was subsequently returned to the laboratory and mated

Animal 50—1 continued in good health with gradually increasing weight for the next several years On January 23, 1955 her weight had reached 46 0 lbs and at this time a rib biopsy was obtained

It will be noted that at no time except during the post partum period of November 28, 1951 to January 29 1952, was there any anemia and this responded very well to the intravenous administration of iron compounds Otherwise there were neither periods involving leucopenia nor notable changes in the differentials, 50—1 remained in an excellent state of health and on November 29 1956 having a weight of 49 lbs was sacrificed for the study of various organs

At autopsy (gross and microscopic examinations were carried out by Drs L L Miller and Thomas Harwood) the subcutaneous tissues and body cavities were normal in appearance The skeletal muscle was a rich deep red color as was the shed blood The parenchymatous organs and the body cavities were un remarkable Sections of bone marrow through the shafts of four or five ribs showed it to be rather spotty with more than the usual amount of fat The femoral and humoral epiphyses upon section showed only a greasy colorless

surface with prominent bony trabeculae The vertebral marrow was moderately cellular Histologically the rib biopsy, taken on January 23rd, 1955 was normally cellular with all hematopoietic series well represented The autopsy histologic material, in two sections of the spleen, showed somewhat smaller than normal malphighian corpuscles Occasional focal accumulations of golden yellow pigment were noted chiefly in the areas of the red pulp The liver was of entirely normal architecture The pancreas and kidney were essentially normal, as were the adrenal gland, thyroid and parathyroid The aorta showed no remarkable changes Lymph nodes from the pulmonary hilar region were unremarkable, except for dense accumulation of deep brown black pigment seen chiefly in the medullary phagocytic cells A section of ovary revealed normal follicle development with a regressing corpus luteum Autopsy of bone marrow in sections of the femoral and humoral epiphyses, was without note, the marrow cavities being replaced nearly entirely with fatty areolar tissue Rib sections taken from the costochondral areas showed various degrees of fattiness Other areas, however, were normally cellular with all hematopoietic series well represented Two sections of vertebral bodies revealed normally cellular bone marrow

The above description is essentially the same in all particulars as related to histories and autopsy findings of dogs 50—2 and 50—3, as also of dog 50—5 which was the control animal in this group

Dog 50—2, which died a few hours after a caesarian section was delivered of several dead pups The section was performed because of an over due pregnancy three years after the original injection Dog 50—3, a male, died after a rib biopsy taken on January 23 1955 and death was attributed to a pneumo thorax Otherwise, his clinical history and autopsy findings were the same as those of the other dogs in the litter

The second litter of animals, injected with variable amounts of the $^{55}$Fe, although studied for slightly shorter periods, showed essentially the same normal growth and development as did the first litter studied Hematologic studies during life were normal At time of sacrifice the remaining dogs of this litter, just as in the first group of dogs, showed no gross or histological changes that were felt to be significant It should be noted that this second litter received much higher doses of iron radioactivity than the first group of dogs — as much as six times on a $\mu$C/kg basis in the case of one animal

In general it is concluded that the mortality of the treated animals which did not survive, as well as that of their progeny resulting from inbreeding was probably in all cases unrelated to any effects from months of irradiation derived from a high titre of $^{55}$Fe in the circulation

## Discussion

We do not have figures available as to the half path in tissues of the very soft beta particle of the isotope used It is difficult to even hazard a guess as to

how many cell diameters such beta particles might traverse before causing ionization On the one hand it might be felt that most of the radiation effect would be accomplished within the confines of the vascular system However in some respects this could be construed to mean fairly general body irradiation with the possible exception of certain fatty tissues for instance Again one must recognize the high degree of vascularity of the liver and spleen where temporary sequestration of red cells perhaps occurs, especially in some sinuses Further more during several life cycles of the red cell the iron is certainly deposited in some elements of the hematopoietic system for matters of hours, or possibly days However, from earlier work we are fairly well convinced that the re utilization of iron following destruction of hemoglobin and re incorporation into a new hemoglobin molecule is very rapid (1) (2)

We must not forget the fact that the greatest part of the retained isotope is in the erythrocyte which is a fairly specialized type of cell Having no nucleus in its adult stage where the isotope is carried for a period of 120 days there is little reason for anticipating radiation changes in a cell which in itself is non reproductive It has been estimated by MARINELLI, QUIMBY & HINE (3) that 24 $\mu$C would probably represent a safe level in the red cell mass of a human donor The amounts used in these experiments would thus represent many hundred times as much radioactivity

With the present state of knowledge of radiobiology it would be pure specula tion to go further in an attempt to determine the lack of radiation effects in the animals studied here

## SUMMARY

Two groups of litter mate dogs were injected with iron containing the Fe isotope at levels ranging from 0 74 to 3 3 mC (70 to 435 $\mu$C/kg) during active growth The animals were followed for periods of four and a half to six years respectively complete blood examinations being conducted at monthly intervals They developed normally and showed no clinical or hematologic changes up to the time of sacrifice

## ZUSAMMENFASSUNG

Zwei Gruppen von jungen Hunden je vom selben Wurf erhielten Eisen Einspritzungen von Fe in Dosen von 0 74 bis 3 3 mC (70 bis 434 $\mu$C/kg) wahrend ihrer Wachstumsperiode Die Tiere wurden uber einen Zeitraum von 4 1/2 bis zu 6 Jahren mittels monatlichen Blutunter suchungen beobachtet Die Hunde erwiesen sich als normal und zeigten keinerlei klinische oder hamatologische Veranderungen wahrend ihres Lebens

## RÉSUMÉ

Deux groupes de jeunes chiens de la même portée ont reçu au cours de leur croissance une injection de fer contenant une dose de l isotope Fe comprise entre 0 74 et 3 3 mC (70 a 434 $\mu$C/kg) Ces animaux ont été observés pendant des périodes allant de quatre ans et demi a six ans subissant un examen hématologique complet tous les mois Ils se sont développés normale ment et n ont présenté aucune anomalie clinique ni hematologique jusqu au moment ou ils ont été sacrifiés

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# DETERMINATION OF INTEGRAL ABSORBED DOSE FROM EXPOSURE MEASUREMENTS

by

Carl Carlsson

The integral absorbed dose (for brevity the term 'absorbed' will usually be omitted) is defined as the mass integral of the absorbed dose, integrated over the total body, or simply as the energy absorbed by the body during radiation treatment or examination

$$\Sigma = \int_M D \, dm \qquad (1)$$

where $\Sigma$ is an integral absorbed dose $D$ absorbed dose $M$ the total mass and $dm$ is a mass element

If the mass is measured in gram and the absorbed dose in rad the integral dose will be expressed in g rad units 1 g rad = 100 erg = $10^{-5}$ joule

(The names and symbols for radiation quantities and units used in this work have been chosen according to ICRU 'Radiation quantities and units 1962')

According to the definition the integral dose can be computed from measurements of the absorbed dose by several detectors uniformly spread throughout the body This measurement naturally cannot be performed in man but with a convenient phantom this and other methods can be used to calibrate an external measuring instrument A large plane parallel ionization chamber is often used (Reinsma 1962 Arnal & Pychlau 1961, Zieler 1960, Carlsson) The chamber is placed between the adjustable diaphragm of a roentgen tube and the patient and measures in the absence of a scattering medium the product

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of the exposure in air and the field area (more exactly the field integral of the exposure in air)

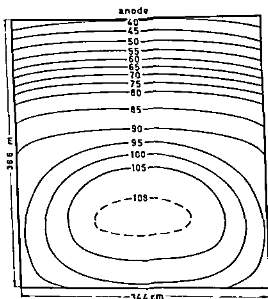
Methods for calculating integral doses from known exposure and field area have been derived by many authors MAYNEORD (1940) attacked the problem in two ways first by depth dose measurements in a phantom and secondly by calculating the incident radiation energy from known energy absorption coefficients for air and measured values of the exposure and field area In the following, these two methods will be further analyzed

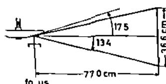
## I Calculation of integral absorbed dose from depth-dose measurements

Measurements according to the definition of the integral dose have been made by MAYNEORD & CLARKSON (1944) They determined integral doses in a man equivalent phantom built of wax and rice, in which several ionization chambers were placed BOAG (1945) used a man shaped phantom, the celluloid man This consists of several plane parallel ionization chambers in which the electrodes also function as phantom material The same phantom was also used by BEWLEY et coll (1959) in determining the integral doses from 200 kV and 8 MV radiation The celluloid man obviates the time consuming work of constructing isodoses or adding many products of mass and absorbed dose Instead one has, among other things, to correct for the different incidence angles of the radiation (because of the lamination) and for the fact that the wall material (cellulose acetate) in the ionization chambers causes the sensitivity of the chamber to decrease at the lowest HVT (1 to 4 mm Al) which are of interest here Chemical dosemeters are very satisfactory from the point of view of the definition integral but their applications are restricted considerably as they suffer from one or more of the following disadvantages low sensitivity, great energy dependence, especially for low energy roentgen radiation and rigorous demands on the purity of the chemicals and vessels used

To measure on the basis of eq 1 as the cited authors have done, is free from objections in principle but is so laborious that one hesitates to use such a method to calibrate an outer detector for various filters, tube potentials wave forms, field areas, and focus skin distances especially as the uncertainty in the determination of the low dose rates outside the geometrical radiation beam can easily be great As the dimensions of the phantom used do not correspond to all cases where determinations of integral doses are of interest, the above mentioned measurements had to be made with many different phantoms

The energy losses in lateral scattering are relatively small (ZIELER 1961) According to BEWLEY et coll (1959) they reach about 8 per cent of the incident energy at a HVT of 1 8 mm Cu and a field diameter of 10 cm, if the phantom is a 23 cm high truncated water cone with a smallest diameter of 25 cm They estimate the back scattered and the transmitted energies as 19 and 17 per cent,



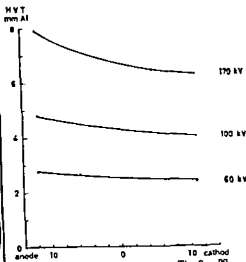




Fig 2

Fig 1 (left) Measured values for exposure in air from a diagnostic roentgen tube 75 kV and HVT = 4 3 mm Al

Fig 2 Variation of HVT with emission angle from a diagnostic roentgen tube

respectively If this phantom is replaced by a water slab of the same thickness but with an infinite lateral extent one part of the radiation losses through the sides of the cone will after multiple scattering processes in the slab appear as back scattered or transmitted radiation and the deviation will be less than the above mentioned 8 per cent The deviation will be still less at low HVT or if the edges of the field are more distant from the lateral limits of the phantom than in the above mentioned example (this is generally valid in the longitudinal direction of the body when the trunk is irradiated) This idealized phantom (the water slab) opens the way to simplified calculations of the integral dose via central axis depth dose data and makes simple comparisons between different calculation methods possible The thickness of the slab is of course easily variable The well known approximate formula of MAYNEORD (1940) estimates the integral dose via central axis depth dose data and integration over the geometrical beam The drawbacks of this method may be overcome by always choosing the depth dose values for the calculations from very large fields (the saturated scatter method) independent of the size of the topical fields (HAPPEY 1940 and 1941 LOEFFLER 1956 SCARPA 1960) To elucidate this latter method we may consider a small roentgen pencil which is a part of and in the centre of

a large, uniform beam, incident on a large phantom The field is so large that a further enlargement does not affect the central axis depth doses The contribution from the small pencil to the integral dose is easily calculated by integrating the dose over that mass which is enclosed by the geometrical limitation of the pencil, as the energy that is lost by photons scattered out of this volume is just compensated by photons scattered in If instead the same pencil alone irradiates the phantom, it will of course cause the same integral dose but this will be strongly underestimated by integrating the central axis depth doses over the mass within the volume of the pencil The mass integral of the dose must instead be extended over the whole phantom to give the same result

As, owing to radiation quality and phantom thickness, very large fields are often required to assure saturation of the scattered radiation at greater depths, it may be difficult to use the method MEREDITH and NEARY (1944) have proposed a method of constructing isodose curves which makes it possible to extrapolate depth doses to infinite field areas The method has only been applied for radiation qualities used in conventional roentgen therapy, and data are lacking for its application with radiation qualities common in diagnostic radiology TROUT et coll (1952) have measured central axis depth doses for radiation qualities with HVT in the region 0 7 to 4 8 mm Al These measurements were performed with a field having the dimensions $36 \times 43$ cm$^2$ Field dimensions and radiation qualities give rise to the presumption that these measurements could be used for calculating integral doses according to the saturated scatter method However, it should be pointed out that the exposure rate from a lightly filtered diagnostic tube with small anode angle is far from homogenous over the whole field An example of measurement of the distribution of the exposure in air from a diagnostic tube is shown in Fig 1 The field dimensions and focus skin distance are about the same as given by TROUT Apparently the exposure varies in the field by more than a factor of two The integral $\int_A \lambda \, dA$ of the exposure, $\lambda$, over the field area, $A$, calculated from Fig 1 is 13 per cent less than if the whole field had been irradiated with the exposure of the central ray With the aid of depth dose data for different field areas the dose contributions from scattered radiation from different parts of the field to the doses of the central ray can be calculated From this it is possible to compute the effect of the exposure variations of the field on the doses of the central ray

The integral doses calculated from central axis depth doses for an inhomogenous field (Fig 1) and for a homogenous field with the same central axis dose at zero depth and with the same radiation quality have been compared, the calculated integral dose for the inhomogenous field is only about 3 to 4 per cent below that for the homogenous field If consideration is taken of the fact that the radiation quality also depends on the direction, the difference will be still less Fig 2 shows how the HVT varies with the direction of the radiation along the axis of the roentgen tube, as measured by the author Another serious

objection to using these depth dose measurements is that they have been made with a large ionization chamber (the Victoreen thimble chamber) The insertion of an air volume in the phantom material causes an increase in measured exposure because of the decreased filtration of both the primary and scattered radiation but also a diminished exposure contribution because of the elimination of scattered radiation from the displaced volume This volume effect of the ionization chamber may lead to corrections in the measured depth doses by several per cent (LIDEN 1961, SKOLDBORN 1959) Usually a large ionization chamber causes an overestimate of the depth doses as well as of the integral dose calculated from them The effects of an inhomogenous field and a large ionization chamber may to a great extent cancel each other

From the experimental values of TROUT et coll the author has calculated integral doses as follows

$$\Sigma = \int_M D dm = \int_0^d \bar{f} X \varrho A_x dx = \bar{f} \varrho A_0 \int_0^d X \left(\frac{F+x}{F}\right)^2 dx \qquad (2)$$

where $f$ = $f$ factor = the ratio between the absorbed dose and the exposure for monoenergetic photons in water

$\bar{f}$ = the average value of the $f$ factor for the photon spectrum in the phantom The values of $\bar{f}$ have been taken from National Bureau of Standards Handbook 78 (1961) and are given in Table 1

$X$ = the exposure in the central ray at the depth $x$

$\varrho$ = the density of the phantom material

$A_0$ = surface area of the field $A$ = the field area at the depth $x$

$F$ = focus—skin distance

$x$ = the depth in the phantom

If $X$ is expressed as a fraction of the exposure measured in the centre of the beam at the position of the phantom surface but with the phantom removed if $A_0$ is chosen as 1 cm² and if the phantom material has the density 1 g/cm³ eq 2 may be simplified to

$$\Sigma = \bar{f} \int_0^d X \left(\frac{F+x}{F}\right)^2 dx g \ \text{rad/(cm}^2 \ \text{R)} \qquad (3)$$

This integral has been evaluated for $d$ = 20 cm for fifteen cases with HVT between 0 91 and 4 8 mm Al The results are presented in Table 1 in the column $\int_0^{20}$ For the calculation of $X$ according to the method of MEREDITH & NEARY the contribution from the primary radiation has been taken from depth dose values for zero area ( Depth Dose Tables for Use in Radiotherapy 1961) and the saturated scatter from HORSELEY & ASPIN (1956)

As earlier the integral

$$\Sigma = \bar{f} \int_0^d (P+M) \left(\frac{F+x}{F}\right)^2 dx \qquad (4)$$

was determined graphically (the results being given in Table 1 for $d$ = 20 cm) $P$ = exposure from the primary radiation $M$ = saturated scatter both are expressed as fractions of the primary exposure at zero depth

Eqs 3 and 4 are approximately independent of the focus-skin distance For a semi infinite phantom the integral dose per cm² and R will be slightly less for a shorter focus skin distance (even if the exposure is constant over the whole surface) owing to the fact that the backscattered energy increases with the obliquity of the incident rays (BERGER & RASO 1960)

**Table 1**

*Integral dose and fractional transmission calculated from depth dose values*

| | kV | Added filter mm | HVT measured mm | $\int_0^{20}$ | $\int_0^{\infty}=\Sigma_\infty$ | $\Gamma_{10}$ | $\Sigma_{10}$ | $\Sigma_{15}$ |
|---|---|---|---|---|---|---|---|---|
| | | | | g rad cm$^{-2}$ R$^{-1}$ | | | | |
| TROUT et coll | 85 | 0 Al | 0 91 Al | 4 9 | 5 0 | 0 1 | 4 2 | 4 7 |
| | 85 | 0 5 Al | 1 35 Al | 6 0 | 6 0 | 0 2 | 4 7 | 5 5 |
| | 85 | 1 0 Al | 1 54 Al | 6 9 | 7 2 | 0 3 | 5 5 | 6 5 |
| | 85 | 2 0 Al | 1 95 Al | 8 2 | 8 6 | 0 5 | 6 3 | 7 5 |
| | 85 | 3 0 Al | 2 50 Al | 9.2 | 9 8 | 0 8 | 7 0 | 8 3 |
| TROUT et coll | 100 | 0 Al | 1 00 Al | 6 7 | 7.2 | 0 7 | 4 9 | 6 0 |
| | 100 | 0 5 Al | 1 60 Al | 7 7 | 8 2 | 0 7 | 5 7 | 6 9 |
| | 100 | 1 0 Al | 1 95 Al | 8 9 | 9 6 | 0 9 | 6 5 | 7 9 |
| | 100 | 2 0 Al | 2 90 Al | 10 6 | 11 8 | 1 5 | 7 4 | 9 2 |
| | 100 | 3 0 Al | 3 60 Al | 11 9 | 13 2 | 1 6 | 8 1 | 10 3 |
| TROUT et coll | 130 | 0 Al | 1 20 Al | 7 4 | 7 9 | 0 6 | 5 3 | 6 6 |
| | 130 | 0 5 Al | 1 95 Al | 9 3 | 10 3 | 1 2 | 6 4 | 8 0 |
| | 130 | 1 0 Al | 2 90 Al | 10 8 | 12 1 | 1 7 | 7 2 | 9 7 |
| | 130 | 2 0 Al | 4 1 Al | 12 4 | 14 1 | 2 1 | 8 1 | 10 6 |
| | 130 | 3 0 Al | 4 8 Al | 13 6 | 16 2 | 3 2 | 8 4 | 11 2 |
| MEREDITH NEARY | — | — | 0 5 Cu | 17 3 | 21 1 | 4 8 | 9 6 | 13 7 |
| | — | — | 1 0 Cu | 20 4 | 26 6 | 7 6 | 10 1 | 15 3 |
| | — | — | 2 0 Cu | 20 9 | 28 2 | 9 1 | 9 6 | 15 7 |
| | — | — | 3 0 Cu | 20 2 | 28 7 | 10 6 | 8 8 | 14 2 |
| | — | — | 4 0 Cu | 18 8 | 27 8 | 11 3 | 7 8 | 12 8 |

$\Sigma_d$ means integral dose per cm² and R in a $d$ cm thick water slab $\int_0^d$ means $\int_0^d \bar{f} X \left(\frac{F+x}{F}\right)^2 dx$ See eqs (3) and (4)

The results $\Sigma$ are corrected for errors in depth doses owing to the fact that they are measured in a phantom thicker than $d$ cm. $T_d$ means energy transmitted per incident cm² and R

$\frac{T_d}{E_f}$ means fraction of the incident energy which is transmitted through a $d$ cm thick water slab

In a water slab with finite thickness the transmission decreases with shorter focus skin distance owing to the longer path in the phantom These phenomena are however of small importance at ordinary focus skin distances, and as they mainly refer to the boundary rays they have only a small effect on the central axis depth doses and the integral dose calculated from them

Therefore eqs 3 and 4 may be evaluated most easily with depth doses measured as tissue air ratios The tissue air ratio is independent of the focus skin distance and equivalent to the infinite focus skin distance in eqs 3 and 4 (JOHNS et coll 1958)

Fig 3 gives for roentgen radiation of HVT = 0 5 mm Cu the central axis

**Table 1** *(cont)*

| $\Sigma$ | $\Sigma_{15}$ | $\Sigma_{30}$ | $\frac{T}{\Sigma_\infty}$ | $\frac{T}{E_f}$ | $\frac{T_{15}}{E_f}$ | $\frac{T}{E_f}$ | $\frac{T}{E_f}$ | $\frac{T_{30}}{E_f}$ | $AE_0$ | $\bar{f}$ rad R |
|---|---|---|---|---|---|---|---|---|---|---|
| g rad cm⁻ R⁻¹ | | | | | | | | | | |
| 4.9 | 5.0 | 5.0 | 0.018 | 0.13 | 0.04 | 0.014 | 0.004 | 0.001 | 0.23 | 0.932 |
| 5.8 | 5.9 | 6.0 | 0.034 | 0.16 | 0.07 | 0.076 | 0.010 | 0.004 | 0.23 | 0.932 |
| 6.9 | 7.0 | 7.1 | 0.046 | 0.18 | 0.08 | 0.035 | 0.016 | 0.007 | 0.23 | 0.932 |
| 8.1 | 8.4 | 8.5 | 0.053 | 0.21 | 0.10 | 0.048 | 0.023 | 0.011 | 0.23 | 0.932 |
| 9.0 | 9.4 | 9.6 | 0.078 | 0.22 | 0.12 | 0.060 | 0.031 | 0.016 | 0.23 | 0.932 |
| 6.6 | 6.9 | 7.0 | 0.091 | 0.24 | 0.13 | 0.070 | 0.037 | 0.020 | 0.24 | 0.932 |
| 7.6 | 7.9 | 8.1 | 0.084 | 0.24 | 0.13 | 0.064 | 0.032 | 0.017 | 0.24 | 0.932 |
| 8.7 | 9.2 | 9.4 | 0.091 | 0.25 | 0.13 | 0.069 | 0.036 | 0.018 | 0.24 | 0.932 |
| 10.3 | 10.9 | 11.3 | 0.13 | 0.28 | 0.17 | 0.10 | 0.058 | 0.035 | 0.24 | 0.932 |
| 11.6 | 12.3 | 12.7 | 0.12 | 0.29 | 0.16 | 0.090 | 0.050 | 0.028 | 0.24 | 0.932 |
| 7.3 | 7.6 | 7.8 | 0.08 | 0.25 | 0.13 | 0.06 | 0.028 | 0.013 | 0.24 | 0.932 |
| 9.0 | 9.6 | 9.9 | 0.12 | 0.29 | 0.17 | 0.09 | 0.050 | 0.027 | 0.24 | 0.932 |
| 10.5 | 11.2 | 11.6 | 0.14 | 0.31 | 0.18 | 0.10 | 0.059 | 0.034 | 0.24 | 0.932 |
| 12.0 | 12.8 | 13.3 | 0.15 | 0.32 | 0.19 | 0.11 | 0.068 | 0.040 | 0.24 | 0.932 |
| 13.0 | 14.1 | 14.8 | 0.20 | 0.36 | 0.23 | 0.15 | 0.098 | 0.063 | 0.24 | 0.932 |
| 16.3 | 18.0 | 19.1 | 0.23 | 0.41 | 0.26 | 0.17 | 0.11 | 0.07 | 0.25 | 0.94 |
| 18.9 | 21.3 | 23.0 | 0.29 | 0.47 | 0.32 | 0.22 | 0.15 | 0.10 | 0.25 | 0.95 |
| 19.1 | 21.8 | 23.7 | 0.32 | 0.49 | 0.34 | 0.24 | 0.17 | 0.12 | 0.25 | 0.95 |
| 18.1 | 21.0 | 23.0 | 0.37 | 0.53 | 0.39 | 0.28 | 0.21 | 0.16 | 0.23 | 0.96 |
| 16.5 | 19.3 | 21.5 | 0.41 | 0.57 | 0.43 | 0.32 | 0.24 | 0.18 | 0.21 | 0.96 |

depth exposure $X$, expressed as a fraction of the incident exposure in air and multiplied by the factor $\left(\frac{F+x}{F}\right)^2$ as a function of the depth in water The expression $\left(\frac{F+x}{F}\right)^2 dx$ constitutes a volume element with the incident area = 1 cm² The integral $\int_0^d \bar{f}\, X \left(\frac{F+x}{F}\right) dx$ expresses a volume dose Multiplication by the density of the phantom gives the integral absorbed dose per cm² and roentgen unit according to eq 3

According to the saturated scatter method the integral dose will be under estimated if the central axis depth doses do not have a saturated contribution of scattered radiation The upper curve in Fig 3 which was calculated according to MEREDITH & NEARY (infinite field area) meets the saturation conditions, and the area beneath the curve is a measure of the integral dose The other curves which refer to depth doses from finite fields underestimate the integral dose to an increasing extent as the field area and thus the contribution

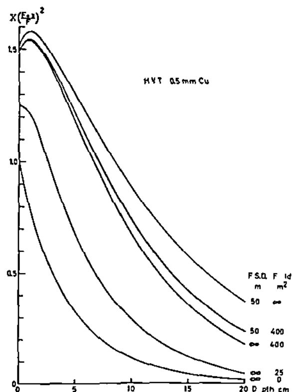
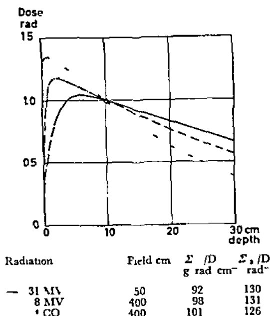



Fig 3 The integrand in eqs (3) and (4) Upper curve represents depth doses with a saturated scatter contribution The area beneath this curve is proportional to the integral dose For doses from a decreasing field area eq (3) underestimates the integral dose to an ever increasing extent

of scattered radiation to the measured depth doses gradually decreases In succession from top to bottom the different areas beneath the curves under estimate the integral dose by 12, 17, 53, and 75 per cent Calculations of the integral dose based on depth dose values and integration over the geometrical cone of radiation can easily result in errors of a factor 2, and in extreme cases even a factor 4, if the saturation conditions are not fulfilled

Of the two cases in Fig 3 with the same incident area (400 cm²) but different focus skin distances (50 cm and infinity), the field with the shorter focus skin distance best meets the saturation conditions since the field area in this case increases with the depth and the relative contribution of scattered radiation to a point at a depth $x$ is dependent of the area of the field at this depth and is independent of the divergence of the radiation (JOHNS et coll 1958) MAYNEORD s well known and often applied formula differs from eq 3




| Radiation | Field cm | Σ /D g rad cm⁻ | Σ₃ /D rad⁻ |
|---|---|---|---|
| — 31 MV | 50 | 92 | 130 |
| 8 MV | 400 | 98 | 131 |
| • CO | 400 | 101 | 126 |

Fig 4 Ratio of integral dose to tumour dose for three radiation qualities

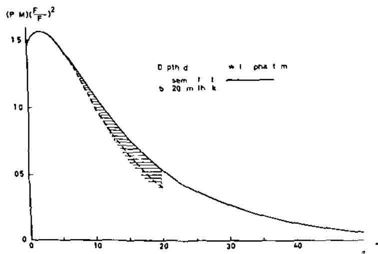



Fig 5 Depth doses in a semi infinite medium and n a 20 cm thick water slab The crossed area corresponds to the energy scattered backwards through the 20 cm plane in the sem nfinite med um Of this energy a fract on is scattered forward over the same plane and so on The broken curve gives the depth doses in the slab

in the approximation of the depth dose as exponentially decreasing in order to obtain a definition integral which can be evaluated.

This and similar methods therefore underestimate the integral doses in the same way as the graphical method presented here. This graphical method has besides greater accuracy the advantage of being easily applicable to high energy radiation where the dose is far from exponentially decreasing. For particle as well as photon radiation of sufficiently high energy the forward scattering dominates to the extent that saturation of the central axis depth doses will be reached for the moderate field areas reported in the standard tables. Fig. 4 gives a comparison of integral doses from $^{60}Co$, 8 and 31 MV roentgen radiation for the same tissue (tumour) dose at a depth of 10 cm. The dose values have been taken from tables for infinite focus skin distance ('Depth dose tables for use in radiotherapy', 1961). It is seen that the 31 MV radiation gives the lowest and $^{60}Co$ the highest integral dose for a 20 cm thick phantom. For a 30 cm thick phantom and the same tumour depth the $^{60}Co$ radiation is preferable.

As the phantom used for the depth dose measurements is usually semi infinite or at least 30 cm deep, the measured depth doses will be larger than if they had been measured in a phantom with smaller dimensions. This is because one part of the dose contribution in the measurement in the thicker phantom originates from radiation that has been backscattered from deeper parts of the phantom. If the integrand $\bar{J}\lambda\left(\frac{F+x}{F}\right)^2$ is extrapolated to infinite depth, i.e. by supposing the whole expression to be exponentially decreasing and then integrated graphically, first over the actual depth 0–$d$, and secondly integrated numerically from $d$ to infinity, then the integral dose to the depth $d$, calculated in this way can be corrected by considering the energy albedo. The energy albedo $A_E$ is defined as the ratio between the reflected and the incident energy. Albedo values for semi infinite media of different materials have been calculated by the Monte Carlo method (BERGER & RASO 1960) for photon energies between 20 keV and 2 MeV and different incidence obliquities.

Fig. 5 gives one example of the integrand in eq. 4 in a semi infinite phantom (solid curve). The broken line refers to the same integrand measured in a phantom $d$ cm thick. In the figures, $d$ has been chosen as 20 cm because this thickness corresponds well with the mean value of the thickness of the trunk in the antero posterior direction in adults. Of the energy $T_d$ which is transmitted in a phantom of thickness $d$, the fraction $A_{Ft}$ is reflected if the depth of the phantom is increased to infinity. However the fraction $A_F$ is backscattered from the first $d$ cm of the phantom, and so on. $A_{Ft}$ is the mean energy albedo value determined from the energy and direction of the photons.

For the calculation of the transmitted energy $T_d$ in a water slab of thickness $d$ from dose values measured in a semi infinite phantom eq. 5 is valid (for brevity the integrand from eqs. 3 and 4 is omitted).

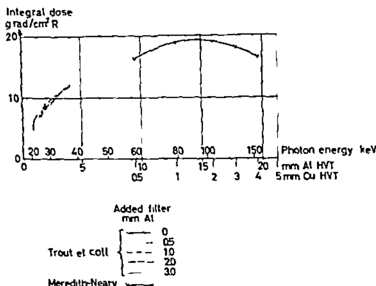



Fig 6 Calculated integral doses in a 20 cm thick water slab as a function of the HVT in mm Al

$$\int_d^{\infty} = T_d - A_{E1} T_d + A_{E_2} A_{E1} T_d - A_{E3} A_{E_2} A_{E1} T_d + \qquad (5)$$

This series converges rapidly because $A_E$ as a rule is smaller than 0 3 In the calculations all $A_E$ have been chosen equal to $A_E = A_E = 0\ 25$ This gives

$$\int_d^{\infty} = T_d \sum_{=0}^{\infty} (-A_{E})^{i} \quad \text{or} \quad T_d = (1+A_E) \int_d^{\infty} \qquad (6)$$

The corrected integral dose is then

$$\Sigma_d = \Sigma_\infty - T_d \qquad (7)$$

Eqs 6 and 7 have been solved for different $d$ and are shown in Table 1 The transmission is th re expre sed as a fraction partly of the integral dose in a semi infinite phantom $\left(\frac{T_d}{\Sigma'_\infty}\right)$ and partly of the incident energy $\left(\frac{T_d}{E_f}\right)$ The transmitted and incident nerg e are here normalized to 1 cm² R incident The incident energy fluence per roentgen unit [ rg (cm² R)] is obtained from the relation $\Sigma_\infty = E_f (1 - A_{E0})$ (8)

where the energy albedo $A_{E0}$ of the primary radiation denotes the fraction of energy back scattered from the phantom surface $A_{E0}$ is obtained from the spectral calculations described under next heading and from Table 1

On the basis of the values in Table 1, the integral doses in a 20 cm thick phantom are presented in Fig 6 as a function of HVT in mm Al The other two

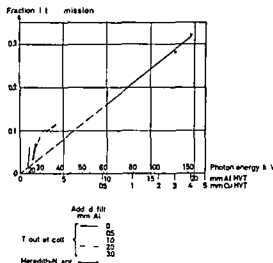



Fig 7 Fraction of the energy transmitted through a 20 cm thick water slab The lower the filtration the higher the transmission for low HVT

scales HVT in mm Cu and keV, are both related to the first scale in a manner that is valid for monoenergetic photons Fig 7 presents in the same way the transmission through a 20 cm thick water phantom For low HVT a tendency to higher integral dose and transmission can be seen for lightly filtered radiation This is due to the fact that the HVT in these cases underestimates the average energy of the radiation We shall return to this question in the following

## II Calculation of the integral absorbed dose by determination of the incident energy

The incident energy can be measured directly by calorimetric methods Simultaneous measurement of the exposure allows the determination of the energy fluence necessary to give one roentgen in free air The expression energy fluence means the time integral of the energy flux density and has the dimension energy per area (ICRU 1962) A calorimetric determination of the energy fluence per roentgen unit with the radiation qualities in which we are interested here has been reported by LAUGHLIN & GENNA (1956) They used roentgen apparatus with potentials between 130 and 400 kV and HVT between 5 1 mm Al and 3 0 mm Cu (see Table 2 and Fig 8)

Measurements of spectra of primary roentgen radiation, which have been reported by, among others, CORMACK et coll (1958 and 1960) and HETTINGER & STARFELT (1958) also give the incident energy These measurements were performed with scintillation spectrometers with various acceleration potentials

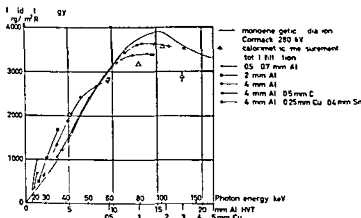



Fig 8 The energy fluence per R for different filtered radiations as a function of the radiation quality For 140 kV radiation with a total filtration of 0 6 mm Al the data for monoenergetic radiation with the same HVT underestimates the incident energy by a factor of 3

and filters in the roentgen apparatus Simultaneous measurements of the exposure were not reported, which explains why the experiments do not directly give the energy fluence per roentgen unit These measurements were performed with a very narrow beam geometry and with intensities so low that exposure measurements under the same conditions would be troublesome

If the energy absorption coefficients for air and the average energy necessary to produce an ion pair in air are known the energy fluence per roentgen unit can be calculated from

$$E_f = \frac{W}{\left(\frac{\mu_e}{\varrho}\right) 300 \cdot 0.001293} \text{ erg cm}^{-2}\text{R}^{-1} \tag{10}$$

where $E_f$ is the necessary energy fluence to give 1 R in air $W$ the average energy dissipated in air to form one ion pair expressed in eV $\left(\frac{\mu_{en}}{\varrho}\right)_{air}$ is the mass energy absorption coefficient for air ($cm^2/g$)

$E_f$ as a function of the photon energy has been calculated by among others MAYNEORD (1940) JOHNS & LAUGHLIN (1956 and MULVEY & BALLINGER (1953) The latter in their work use values of the absorption coefficient from WHITE GROTSTEIN (1957) and their calculations are used in the following However 34 eV will be preferred as a value of $W$ instead of the value 33 eV used by MULVEY & BALLINGER (ICRU 1961 As $W$ is assumed to be a constant over the whole energy interval this involves only a simple correction Newer values of the energy absorption coefficient (R T BERGER 1961) do not appreciably change the results given here

The incident energy can then be calculated from eq 10 if the field area and the exposure in air are measured provided that the photons are monoenergetic By means of eq 10 and measured spectra of primary roentgen radiation the energy fluence per roentgen unit can be calculated for radiation with a continuous spectrum

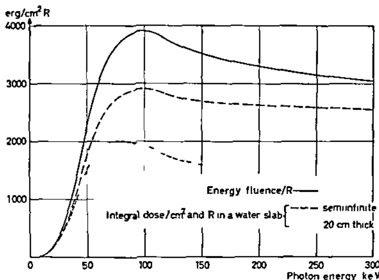



Fig 9 The incident energy per cm² and R (solid curve) as a function of the photon energy For the broken curve the reflected energy is subtracted from the incident For the dotted curve the transmitted as well as the reflected energies are subtracted

If $\varepsilon$ is the energy of the photons $P(\varepsilon)$ the number of normally incident photons with the energy $\varepsilon$ per keV interval and cm² then $P(\varepsilon)\, d\varepsilon$ expresses the number of incident photons per cm² with energies between $\varepsilon$ and $\varepsilon + d\varepsilon$ $\varepsilon P(\varepsilon) d\varepsilon$ erg/cm² expresses the energy fluence of these photons

$\frac{\varepsilon P(\varepsilon) d\varepsilon}{E_f(\varepsilon)}$ expresses the exposure in air which this energy fluence gives

The mean value of the energy fluence per roentgen unit for the whole spectrum is given by

$$\overline{E}_f = \frac{\int_0^\infty \varepsilon P(\varepsilon) d\varepsilon}{\int_0^\infty \frac{\varepsilon P(\varepsilon) d\varepsilon}{E_f(\varepsilon)}} \tag{11}$$

In the calculation of eq 11, $E_f$ as already mentioned, has been taken from MULVEY & BALLINGER with $W = 34$ eV The spectral distributions were first obtained from measured primary spectra (HETTINGER & STARFELT, CORMACK et coll ) and then by calculating new, more heavily filtered spectra from the first mentioned Instead of $P(\varepsilon)$, $P(\varepsilon)e^{-\mu(\varepsilon)d}$ is inserted in eq 11, where $\mu(\varepsilon)$ = the total linear attenuation coefficient for the filter material, $d$ = the linear thickness of the filter, $\mu(\varepsilon)$ has been taken from WHITE GRODSTEIN (1957) Coherent scattering is also included in $\mu(\varepsilon)$ This is reasonable on account of the extreme narrow beam geometry in the spectral measurements

Filter materials and thicknesses have been chosen so that the resulting total

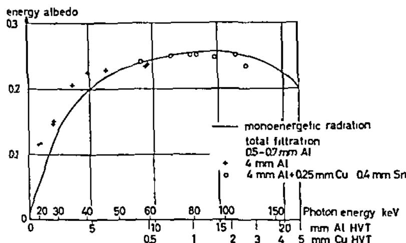



Fig 10 The energy albedo for monoenergetic photons and for roentgen radiation of different filtration

filters (inherent and added) amount to 2 3 and 4 mm Al 4 mm Al + 0 5 mm Cu, and 4 mm Al + 0 25 mm Cu + 0 4 mm Sn The calculations cover radiation qualities used both in roentgen diagnostic examinations and in radio therapy For each of these spectra $E_f$, the energy fluence per roentgen unit and also the half value thickness or half value layer (HVT or HVL), have been calculated for both mm Al and mm Cu HVT is here, as in the preceding section defined as the thickness of an attenuator which is necessary to reduce the exposure or the exposure rate in air by a factor of two In the calculations of the HVT the same absorption coefficients have been used as in the spectral calculations The HVT is obtained from

$$\frac{1}{2}\int_0^\infty \frac{\varepsilon P(\varepsilon)d\varepsilon}{E_f(\varepsilon)} = \int_0^\infty \frac{\varepsilon P(\varepsilon)e^{-\mu(\ )\mathrm{HVT}}d\varepsilon}{E_f(\varepsilon)} \tag{12}$$

In practice instead of HVT different thicknesses, $d$ are tried in eq 12 so that the ratio between the integrals gives values in the neighbourhood of 0 5 Then HVT is obtained by interpolation i e just as in HVT measurements For measurements of HVT defined as in eq 12 a stringent narrow beam geometry is necessary

Fig 8 shows both $\bar{E}_f$ and $E_f$ (monoenergetic photons) as functions of HVT in mm Al The curve without signs corresponds to monoenergetic radiation and the other curves correspond to roentgen radiation with the indicated total filtration The lowest HVT corresponds to the lowest voltage of the roentgen tube Specifications of voltages are given in Table 2 As could be expected the curves for heavily filtered radiation (narrow spectrum) agree best with the curve for monoenergetic photons The greatest deviations are found with light filtrations and tube voltages of about 100 kV

Of course the maxima of the curves for the spectra are inferior to that of the monoenergetic radiation This explains why $\bar{E}_f < E_f$ for HVT greater than 0 5 mm Cu For low HVT, $\bar{E}_f > E_f$, especially at low filtrations In this case, for the HVT measurement of radiation with a broad spectrum, the exposure *is reduced to one half mainly by a strong absorption of low energy photons* These low energy photons provide a large contribution to the exposure but a small contribution to the energy fluence, and therefore the spectrum is alloted an effective energy (its HVT) lower than its energy fluence and mean energy would indicate

From a knowledge of the total filtration the incident energy can be calculated by means of Fig 8 if the exposure in air and the field area are known As is seen in Fig 8, the agreement between the calorimetric measurements of the energy fluence per roentgen unit and the spectral calculations is surprisingly good in the cases where direct comparisons can be made (130 kVp and 4 1 mm Al total filter and 250 kVp and 0 5 mm Al + 1 5 mm Cu total filter) Also in the other cases the same general trends are to be found as in the spectral calculations i e the broader the spectrum the greater the deviations from the monoenergetic curve

The integral dose is obtained from the incident energy by subtraction of backscattered and transmitted radiation energy

The fraction of the energy scattered backwards is taken from the energy albedo calculations of BERGER and RASO (1960) and the fraction of the energy transmitted from the calculations in section I Fig 9 gives for monoenergetic radiation (a) the energy fluence per roentgen (b) the integral dose in a semi infinite water medium (backscattered energy subtracted from (a) (c) the integral dose in a 20 cm thick water slab (the transmitted energy subtracted from (b))

The integral doses and the backscattered and transmitted energies in (b) and (c) are per cm² and roentgen unit The transmission calculations are performed for continuous spectra and are not strictly valid for monoenergetic photons As a further criticism may be mentioned that the backscattered energy from a water slab will be slightly overestimated because it has been calculated for a semi infinite phantom According to BERGER & DOGGETT (1956) the reflection from a barrier will rapidly assume its maximum value A water slab with a thickness of two mean free paths of the primary photons (0 66 MeV) is already equivalent to a semi infinite medium LEIMDORFER (1963) has shown that to reach the maximum value of reflected energy in concrete a greater thickness in mean free paths is required at lower photon energies in the range 1 to 10 MeV From backscatter measurements by HETTINGER (1960) it is evident that at least 3 mean free paths are necessary at photon energies as low as between 60 and 100 keV A mean free path (mfp) in water is for 60 keV photons 4 9 cm and for 200 keV photons 7 3 cm Then the 20 cm thick water slab is at least 3 to 4 mfp for most of the spectra considered here The

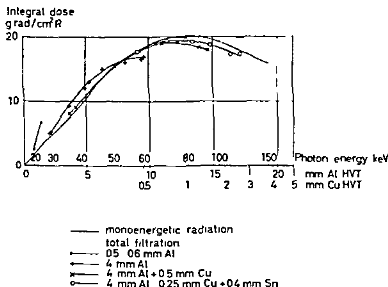



Fig 11 Integral doses per cm and R in a 20 cm thick water slab as a function of the radiation quality

overestimate of the reflection in the calculations is then slight and only at the highest energies may one expect slightly underestimated integral doses

For all the spectra in Table 2 a mean energy albedo $\bar{A}_E$ has been calculated as

$$\bar{A}_E = \frac{\int_0^\infty A_E(\varepsilon)\varepsilon P(\varepsilon)d\varepsilon}{\int_0^\infty \varepsilon P(\varepsilon)d\varepsilon} \tag{13}$$

In Fig 10 both $A_E$ (monoenergetic photons and $\bar{T}_E$ for the different filtered radiation are presented as functions of the HVT in aluminium The reflected and transmitted energies have been subtracted from the incident energy from the different spectra according to

$$\Sigma \quad = \frac{\int \{[1 - A_E + \quad ]\varepsilon P(\varepsilon) - T_0 \quad \varepsilon \quad \} d\varepsilon}{\int \frac{\varepsilon I(\varepsilon) d}{E_f(\varepsilon)}} \tag{14}$$

The results integral doses in a 20 cm thick water slab are presented in Table 2 and Fig 11

## III Comparison between different estimations of integral doses

From Fig 12 which is a combination of Figs 6 and 11 calculations of integral doses from depth dose data and primary spectra can be compared From both methods it is obvious that the HVT concept measured in mm Al

**Table 2**

*Integral dose calculations from spectral measurements*

| Spectrum (The term calculated means calculated by the author from the measured spectrum ~ means alternating voltage) | | kV | Total filtration mm | HVT | |
|---|---|---|---|---|---|
| | | | | Calculated | |
| | | | | mm Al | mm Cu |
| Hettinger Starfelt | measured | 45 | 0.7 Al | 1.00 | 0.030 |
| | calculated | 45 | 2.0 Al | 1.50 | — |
| | » | 45 | 3.0 Al | 1.80 | |
| | | 45 | 4.0 Al | 2.04 | 0.061 |
| | » | 45 | 4 Al+0.5 Cu | 3.65 | 0.13 |
| | » | 45 | 4 Al+0.25 Cu+0.4 Sn | 2.06 | 0.081 |
| Hettinger Starfelt | measured | 75 | 0.7 Al | 1.35 | 0.04[illegible] |
| | calculated | 75 | 2.0 Al | 2.46 | |
| | » | 75 | 3.0 Al | 3.06 | |
| | » | 75 | 4.0 Al | 3.58 | 0.14 |
| | » | 75 | 4 Al+0.5 Cu | 7.33 | 0.3[illegible] |
| | » | 75 | 4 Al+0.25 Cu+0.4 Sn | 9.09 | 0.4[illegible]0 |
| Hettinger Starfelt | measured | 100 | 4 Al | 4.90 | 0.1[illegible]3 |
| | calculated | 100 | 4 Al+0.5 Cu | 9.3 | 0.50 |
| | » | 100 | 4 Al+0.25 Cu+0.4 Sn | 11.4 | 0.76 |
| Hettinger Starfelt | measured | 145 | 4 Al | 6.33 | 0.30[illegible] |
| | calculated | 145 | 4 Al+0.5 Cu | 11.0 | 0.738 |
| | » | 145 | 4 Al+0.25 Cu+0.4 Sn | 13.4 | 1.1[illegible] |
| Hettinger Starfelt | measured | 170 | 4 Al | 8.13 | 0.4[illegible] |
| | calculated | 170 | 4 Al+0.5 Cu | 12.2 | 1.00 |
| | » | 170 | 4 Al+0.25 Cu+0.4 Sn | 14.8 | 1.[illegible]3 |
| Hettinger Starfelt | measured | 225 | 4 Al | 9.60 | 0.68 |
| | calculated | 225 | 4 Al+0.5 Cu | 13.9 | 1.44 |
| | » | 225 | 4 Al+0.25 Cu+0.4 Sn | 16.4 | 2.27 |
| Hettinger Starfelt | measured | 250 | 4 Al | 9.44 | 0.[illegible]6 |
| | calculated | 250 | 4 Al+0.5 Cu | 14.6 | 1.6[illegible] |
| | » | 250 | 4 Al+0.25 Cu+0.4 Sn | 17.1 | 2.[illegible]4 |
| Hettinger Starfelt | | 50~ | 0.7 Al | 0.74 | 0.092 |
| | calculated | 50~ | 4.0 Al | 1.87 | 0.057 |
| | » | 50~ | 4 Al+0.5 Cu | 3.76 | 0.13 |
| Hettinger Starfelt | | 90~ | 0.7 Al | 1.33 | 0.04 |
| | calculated | 90~ | 4.0 Al | 3.49 | 0.12 |
| | » | 90~ | 4 Al+0.5 Cu | 7.67 | 0.35 |

**Table 2** *(cont.)*

| HVT Measured mm | Energy fluence per roentgen $erg\ cm^{-2}\ R^{-1}$ | Energy albedo per cent | Phantom 20 thick | |
|---|---|---|---|---|
| | | | Transmission per cent | Integral dose per cm and roentgen $g\ rad\ cm^{-1}\ R^{-1}$ |
| | 352 | 11.7 | 3.4 | 3.00 |
| — | 488 | 13.3 | 4.0 | 4.04 |
| — | 56[illegible] | 14.1 | 4.3 | 4.60 |
| — | 672 | 14.7 | 4.6 | 5.00 |
| — | 1 070 | 18.4 | 6.8 | 8.00 |
| — | 599 | 13.7 | 4.4 | 4.90 |
| — | 690 | 17.9 | 5.1 | 5.15 |
| — | 1 030 | 19.6 | 9.4 | 7.30 |
| — | 1 200 | 20.4 | 10.3 | 8.30 |
| — | 1 340 | 20.6 | 10.6 | 9.30 |
| — | 2 410 | 23.[illegible] | 12.8 | 15.4 |
| — | 2 910 | 24.2 | 15.0 | 17.7 |
| 0.19 Cu | 1 830 | 22.5 | 13.0 | 12.1 |
| — | 2 970 | 24.3 | 15.8 | 17.8 |
| — | 3 440 | 25.0 | 18.7 | 19.4 |
| 0.30 Cu | 2 420 | 22.8 | 15.2 | 15.0 |
| — | 3 280 | 24.8 | 17.4 | 18.9 |
| — | 3 650 | 25.[illegible] | 22.0 | 19.[illegible] |
| 0.39 Cu | 2 670 | 23.9 | 16.7 | 15.9 |
| — | 3 370 | 24.[illegible] | 18.6 | 19.1 |
| — | 3 630 | 24.8 | 24.0 | 18.6 |
| 0.55 Cu | 2 850 | 23[illegible] | 17.2 | 16.9 |
| — | 3 420 | 24.1 | 22.3 | 18.3 |
| — | 3 580 | [illegible] | 26.6 | 17.3 |
| 0.69 Cu | 2 7[illegible]0 | 2[illegible] | 1[illegible] | 16.5 |
| — | 3 390 | 23.7 | 23.4 | 1[illegible]9 |
| — | 3 5[illegible]0 | 23.4 | 27.5 | 1[illegible] |
| — | [illegible]0 | 10.5 | 3.1 | [illegible]33 |
| — | 83 | 14.1 | 4.1 | 4.76 |
| — | 1 040 | 18.6 | 6.6 | 8.14 |
| — | [illegible]0 | 18.1 | 8.7 | 4.94 |
| — | 1 360 | 22.5 | 9.9 | 9.20 |
| — | 2 570 | 23.5 | 13.2 | 15.9 |

**Table 2** *(cont.)*

| Spectrum | | kV | Total filtration mm | HVL | |
|---|---|---|---|---|---|
| | | | | Calculated | |
| | | | | mm Al | mm Cu |
| CORMACK | measured | 140 | 0.[illegible] Al | 1.33 | 0.05 |
| | calculated | 140 | 2.0 Al | 3.75 | |
| | » | 140 | 3.0 Al | 4.62 | |
| | | 140 | 4.0 Al | 5.30 | 0.23 |
| | » | 140 | 4 Al + 0.5 Cu | 10.5 | 0.47 |
| | » | 140 | 4 Al + 0.25 Cu + 0.4 Sn | 12.3 | 1.10 |
| CORMACK* | measured | 140 | 0.6 Al | 1.33 | 0.0 |
| | calculated | 140 | 4.0 Al | 5.17 | 0.23 |
| | » | 140 | 4 Al + 0.5 Cu | 10.5 | 0.6 |
| | | 140 | 4 Al + 0.25 Cu + 0.4 Sn | 12.9 | 1.10 |
| CORMACK | measured | 280 | 2 Al + 0.25 Cu + 0.25 Sn | 14.4 | 1.7 |
| | » | 280 | 2 Al + 0.25 Cu + 0.6 Sn | 17.1 | 2.7 |
| | | 280 | 2 Al + 0.25 Cu + 1.2 Sn | 18.1 | 3.10 |
| EHRLICH | measured | [illegible]0 | 0.5 Al | 0.77 | 0.03 |
| | calculated | [illegible]0 | 4.0 Al | 2.03 | 0.08 |
| | » | [illegible]0 | 4 Al + 0.5 Cu | 4.4 | 0.14 |
| | | [illegible]0 | 4 Al + 0.25 Cu + 0.4 Sn | 2.35 | 0.04 |
| LAUGHLIN | measured | 130~ | 1.1 Al | | |
| calorimeter | » | 200~ | 0.1 Al + 0.3 Cu | | |
| | | 2[illegible]0~ | 0.1 Al + 0.35 Cu | | |
| | | [illegible]0~ | 0.5 Al + 1.5 Cu | | |
| | | 400~ | 1 Al + 2.0 Cu | | |

* In the calculations $\left(\frac{\mu}{\rho}\right)_t$ in eq. 10 is taken from R. T. Berger (1961).

does not correspond to a unique integral dose. As in Figs. 6, 7, 8 and 11, Fig. 12 shows that the HVL underestimates the average energy of the spectra in the low energy region.

The agreement between the results of the two calculation methods is rather good, although in the low energy region 1 to 5 mm Al HVL the depth dose calculations result in higher integral doses than the spectral calculations for the same HVL and filtration. As reasons for the deviations may be mentioned:

1. TROUT et coll. (1952) measured their depth doses with a load up to 500 mA of a full wave 60 cycle diagnostic roentgen unit, while the spectral measurements were performed with so low currents, less than 1 mA, that the tube voltage owing to the influence of the cable capacitance (TROUT et coll. 1960) was constant. There probably are a relatively greater number of low energy photons in the radiation from a tube with pulsating voltage. This means that

**Table 2** *(cont.)*

| HVT | Energy fluence per roentgen | Energy albedo | Phantom 20 cm thick | |
|---|---|---|---|---|
| Measured mm | erg cm⁻ R⁻¹ | per cent | Transmission per cent | Integral dose per cm and roentgen g rad cm⁻ R⁻ |
| 1 33 Al | 995 | 21 3 | 12 0 | 6 63 |
| — | 1 680 | 22 3 | 13 0 | 10 9 |
| — | 1 890 | 22 8 | 13 4 | 12 1 |
| — | 2 050 | 23 1 | 13 6 | 13 0 |
| — | 3 200 | 24 6 | 16 8 | 18 8 |
| — | 3 620 | 25 2 | 21 0 | 19 5 |
| 1 33 Al | 1 040 | — | — | — |
| — | 2 130 | — | — | — |
| — | 3 230 | — | — | — |
| — | 3 590 | — | — | — |
| 1 77 Cu | 3 390 | 23 8 | 23 4 | 17 9 |
| 2 63 Cu | 3 530 | 23 5 | 27 5 | 17 3 |
| 3 14 Cu | 3 620 | 23 2 | 29 1 | 17 3 |
| — | 307 | 11 5 | 3 5 | 2 57 |
| — | 649 | 15 1 | 4 7 | 5 20 |
| — | 1 230 | 19 3 | 7 4 | 9 00 |
| — | 794 | 16 8 | 5 8 | 6 00 |
| 5 1 Al | 2 020 | | | |
| 0 5 Cu | 2 840 | | | |
| 1 0 Cu | 3 170 | | | |
| 1 9 Cu | 3 560 | | | |
| 3 0 Cu | 2 850 ± 90 | | | |

the HVT underestimates to an even greater extent the average energy of the radiation, which may explain the whole deviation. In Table 2 a few spectra with pulsating tube voltage (HETTINGER & STARFELT) have been used for integral dose calculations. The expected higher integral dose per cm and roentgen unit than for radiation with the same HVT and filtration but with constant voltage has not been observed with certainty.

2 The relatively large ionization chamber used by TROUT et coll. gives too high values in a phantom.

3 The spectral measurements underestimate the number of low energy photons. The number of low energy photons $P(\varepsilon)$ just as the energy fluence per roentgen unit $E_f(\varepsilon)$ varies rapidly with the energy $\varepsilon$ for the lowest energies which explains the fact that the calculation of eq. 11 is most uncertain for low photon energies.

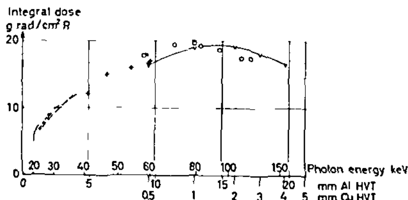



Fig. 12. Combination of figs 6 and 11. The integral doses calculated from depth doses and spectral measurements can be compared.

Integral doses calculated by means of the Meredith Neary method differ less than those based on TROUT et coll. from the spectral calculations (Fig. 12). The method of Meredith Neary gives lower integral doses for HVT beneath 1 mm Cu and higher for HVT over 2 mm Cu than the spectral calculations. The low values may be due to an underestimate of the contribution of the saturated scatter to the depth doses by the above mentioned method. This is indicated by the fact that if the contribution of the saturated scatter is taken from a table for short focus skin distance the calculated integral dose will be greater than for a greater focus skin distance. The integral doses estimated from eq. 3 are greater for a short focus skin distance because the field is [illegible] and thus the contribution of scattered radiation is greater for greater depths (JOHNS et coll.). When the scatter contribution is already saturated one may instead expect the reverse for a short focus skin distance, as in this case the intensity of the border radiation decreases according to the inverse square law. Increased reflection and inhomogeneities in the field also play a role (Fig. 1).

As the energy albedo has been calculated for a semi-infinite phantom the reflection will be overestimated to a greater extent for thinner water slabs. This results in an underestimate of the spectral calculations of the integral doses especially at large HVT. This may be the reason for the lower values of the integral doses calculated from the spectra for the higher HVT. It must be admitted however that the calculations of the transmission are so inaccurate that nothing definite may be said concerning these small deviations.

To compare the calculations with those of other authors the results published by SCARIA (1960), KELLER (1956), REINSMA (1962), and ZIELER (1961) have been added in Fig. 13 to the results from Fig. 12. SCARIA uses the saturated scatter method and his results are approximately identical with the results based on the Meredith Neary method. The calculations of KELLER give

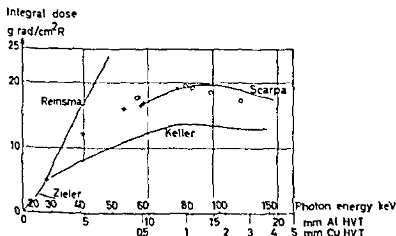



Fig. 13. Integral doses per cm² and R calculated by different authors are added to fig. 12.

appreciably lower results whereas REMSMA simply assumes that all of the incident energy is absorbed. He neglects backscatter and transmission and assumes that the HVT well describes the radiation quality. Neglecting the spectral differences for radiation with the same HVT involves a faulty estimation of the dose-saving effect of the filtration of a roentgen tube. In his measurements of integral doses (properly incident energy) in roentgen diagnostic examinations he uses a roentgen tube with an inherent filtration equivalent to 2 mm Al. He compares measured integral doses without and with an added filter composed of 0.2 mm Cu + 1 mm Al and does not observe any decrease of the integral doses in spite of the fact that the skin doses decrease by a factor of [illegible] for the heavier filter. The decrease of the integral dose (incident energy) produced by the filter is concealed as he underestimates the incident energy more for the unfiltered radiation than for the filtered. This is evident from Fig. 8 where the HVT varies between 1.5 and [illegible] mm Al for unfiltered radiation and between 4 and 9 mm Al for filtered radiation.

ZIELER (1961) also calculates integral doses from exposure measurements and energy absorption coefficients for air. Like REMSMA he chooses for this heterogeneous and low energy radiation an average absorption coefficient taken from monoenergetic radiation with the same HVT. On the other hand he estimates the energy loss due to scattering and transmission in various phantoms. He uses the energy flux density (spherical intensity) instead of the energy current density (plane intensity) in his estimate of the reflected and transmitted energies (BEWLEY et coll. 19[illegible]; [illegible] et coll. 1959; WHYTE [illegible]). The reflected and transmitted energies will then be overestimated by up to a factor 2 which means a grave underestimate of the integral dose.

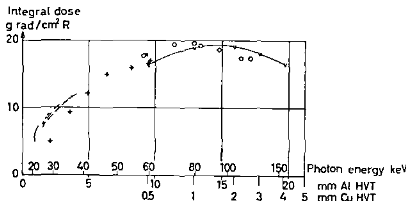



Fig 12 Combination of figs 6 and 11 The integral doses calculated from depth doses and spectral measurements can be compared

Integral doses calculated by means of the Meredith Neary method differ less than those based on TROUT et coll from the spectral calculations (Fig 12) The method of Meredith Neary gives lower integral doses for HVT beneath 1 mm Cu and higher for HVT over 2 mm Cu than the spectral calculations The low values may be due to an underestimate of the contribution of the saturated scatter to the depth doses by the above mentioned method This is indicated by the fact that if the contribution of the saturated scatter is taken from a table for short focus skin distance the calculated integral dose will be greater than for a greater focus skin distance The integral doses estimated from eq 3 are greater for a short focus skin distance because the field area and thus the contribution of scattered radiation is greater for greater depths (JOHNS et coll) When the scatter contribution is already saturated one may instead expect the reverse for a short focus skin distance as in this case the intensity of the border radiation decreases according to the inverse square law Increased reflection and inhomogeneities in the field also play a role (Fig 1)

As the energy albedo has been calculated for a semi infinite phantom the reflection will be overestimated to a greater extent for thinner water slabs This results in an underestimate of the spectral calculations of the integral doses, especially at large HVT This may be the reason for the lower values of the integral doses calculated from the spectra for the higher HVT It must be admitted however that the calculations of the transmission are so inaccurate that nothing definite may be said concerning these small deviations

To compare the calculations with those of other authors the results published by SCARPA (1960) KELLER (1956) REINSMA (1962), and ZIELER (1961) have been added in Fig 13 to the results from Fig 12 SCARPA uses the saturated scatter method and his results are approximately identical with the results based on the Meredith Neary method The calculations of KELLER give

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# AUTORADIOGRAPHIC LOCALIZATION OF STRONTIUM 85 IN OSTEOSARCOMAS

by

I E APPELGREN, A NILSSON and S ULLBERG

The only isotopes that have been used up to now in autoradiographic distribution studies with radiostrontium seem to be $^{90}$Sr and $^{89}$Sr These are both exclusively beta emitters with the relatively high maximum energies of 0 55 and 1 5 MeV respectively

Strontium 85 has been used mainly in experiments connected with external measurements Its 0 513 MeV gamma radiation has then been registered by scintillation detectors $^{85}$Sr also emit short range extranuclear electrons (main energy about 11 5 keV) which theoretically are very suitable for high resolution autoradiography

The present authors in earlier investigations with transplanted bone forming osteosarcomas (3 4) found a more rapid strontium turnover in tumours than in normal bone The autoradiograms revealed a very rapid uptake of $^{89}$Sr in the actively growing tumour tissue soon after injection followed later by a rapid decrease in concentration

In the present investigation the early uptake of radiostrontium in transplanted osteosarcomas has been studied in more detail by means of autoradiography An improved autoradiographic resolution was obtained, mainly

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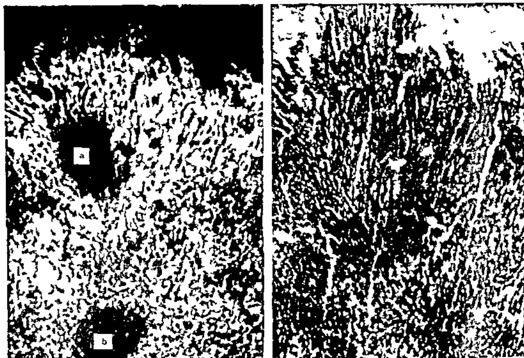


Fig 1 *Left* Autoradiogram of part of a transplanted osteosarcoma 4 hours after injection of Sr hite areas correspond to high radiostrontium uptake high uptake is evident in bone trabeculae two areas (a) and (b) show very low Sr uptake *Right* Section corresponding to the autoradiogram stained with von Kossa's silver heavy mineralization is generally related to Sr uptake the trabeculae in areas corresponding to the Sr free parts (a) and (b) in the autoradiogram are lightly more slender in neighbouring parts of the tumour × 40

because of the more favourable radiation properties of $^{85}$Sr as compared with $^{90}$Sr

*Methods* $^{85}$Sr nitrate in $HNO_3$ solution, was purchased from Oak Ridge Tennessee USA The specific activity was 8 718 mC/g

Inbred CBA mice were used as experimental animals Small pieces (about 2 × 2 × 2 mm) of $^{90}$Sr induced osteosarcomas were transplanted to the subcutaneous dorsal region of the neck of other CBA mice The tumours had been used for transplantation in several generations of animals and had lost their original content of $^{90}$Sr, in two months they had reached a diameter of 2 5 to 3 cm

Strontium 85 (80 $\mu$C) was injected intraperitoneally after development of the transplanted tumour and autoradiograms were obtained of sagittal whole body sections through the mice which were killed four hours later by immersion in a dry ice and acetone mixture

Section thicknesses varied from 5 to 20 $\mu$ The autoradiographic exposure



Fig 2 Transplanted osteosarcoma with highly mineralized tumour bone (lower part of view) and a peripheral narrow zone of soft tumour tissue (upper part of view) where trabecular bone has not yet been formed van Gieson × 100

was made by apposition against Ilford G 5 nuclear plates (emulsion thickness 4 μ), or films of the Schumann type (Kodak SWR) with the silver bromide layer confined to the surface of the emulsion The exposure time was 16 days The autoradiographic method has been described earlier (5, 6) The sections were stained by the von Kossa method after the autoradiographic exposure Sections for histologic examination 5 μ in thickness were also stained with haematoxylin eosin azure eosinate (Lillie) or according to van Gieson

## Results

The most peripheral part of the tumour consists of a narrow zone of a cellular soft tissue without detectable mineralization (Figs 1 and 2) there is no noticeable $^{85}$Sr uptake in this area (Fig 1) The next zone contains well developed mineralized trabeculae (Fig 3) with highly active osteoblasts (Fig 4) and mostly intact blood vessels This area shows the most active uptake of $^{85}$Sr in the autoradiograms

The lines of high uptake of $^{85}$Sr in the autoradiograms correspond well with the bone trabeculae in the von Kossa stained sections (Fig 1) A number of small islands (10 μ to 1 mm in diameter) are seen in the zone of generally intact obviously fast growing tumour tissue and these in the autoradiograms present evidence of little or no uptake of $^{85}$Sr The uptake of $^{85}$Sr gradually rises to match that of the surroundings at the periphery of these dead islands (Fig 1) The degree of mineralization occasionally appears in the corresponding areas of the von Kossa stained sections Similar islands with varying degrees of cellular degeneration from a hardly noticeable granulation of the osteoblasts to complete necrosis of the tumour bone may be found in the histologic sections Fig 5)



Fig. 3. Transplanted tumour. Highly mineralized necrotic area at upper right corner. van Gieson × 100.



Fig. 4. Area from a transplanted tumour with blood vessels, well developed tumour bone and highly active osteoblasts. Azure eosinate × 400.

## Discussion

The use of $^{85}$Sr in autoradiography has led to a striking improvement in resolution compared with earlier experiences with [illegible]Sr. This is probably mainly due to the contribution of the short range extranuclear electrons emitted by $^{85}$Sr (1, 2).

The monoenergetic electrons of $^{85}$Sr have predominant lines at about 11.5 keV, in the neighbourhood of the energy of tritium (max. energy 18 keV). The range for such electrons is 2.2 $\mu$ in water. The electron radiation may be expected to dominate in causing blackening of the photographic emulsion in autoradiography with thin sections and emulsions, in work with sections

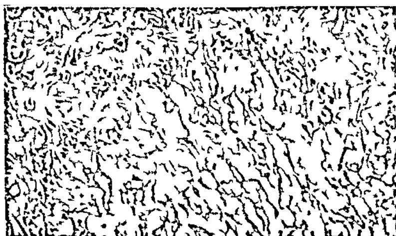


Fig 5 Transplanted osteosarcoma with necrosis of the tumour bone Empty lacunae and debris between the narrow trabeculae van Gieson × 100

considerably thicker than the range of the electrons however it can be expected that the electromagnetic (roentgen) radiation of $^{85}$Sr (energy 13 3 keV) significantly contributes to the blackening of the emulsion If the absorption in water is considered, the roentgen radiation of $^{85}$Sr (half thickness about 3 3 mm) is less advantageous for autoradiographic resolution than the beta radiation of $^{90}$Sr (range about 1 8 mm or half thickness about 0 25 mm) the situation will be the converse however if the absorption in the photographic emulsion is considered With an emulsion consisting of 50 per cent silver bromide and 50 per cent gelatine (v/v) the half thickness of the $^{90}$Sr betas is about 70 μ while that of the 13 3 keV roentgen radiation of $^{85}$Sr is only about 50 μ

Attention has not been paid in the above calculation to the fact that the autoradiographic resolution with $^{90}$Sr is impaired by the influence from the yttrium 90 daughter

Concerning the uptake of radiostrontium in the tissues the results agree with the previous observation of a very high early uptake of radiostrontium in tumour as compared with normal bone The distribution within the tumour tissue however, was highly irregular with marked differences in uptake both between the various zones from the periphery and inwards and within the zones

The appearance of strontium 85 free areas in zones of rapid tumour growth may probably be related to blood vessel damage Autoradiography appears to be a sensitive method for discovering metabolic changes in such areas before any histologic signs can be detected

## Acknowledgement

The authors are indebted to S Forberg Division of Nuclear Chemistry Royal Institute of Technology Stockholm for valuable advice

## SUMMARY

Improved resolution has been obtained with strontium 85 as compared with strontium 90 in autoradiographic investigations of the distribution of radiostrontium in bone forming osteosarcomas A much higher uptake of radiostrontium was found in tumour than in normal bone the distribution being highly irregular and related to the varying degrees of minerali zation and degenerative changes

## ZUSAMMENFASSUNG

Strontium 85 zeigte ein besseres Auflosungsvermogen als Strontium 90 in autoradio graphischen Untersuchungen uber die Verteilung von radio aktiven Strontium in knochen bildenden Osteosarkomen Es ergab sich dass betrachtlich mehr radio aktives Strontium im Tumor als im normalen Knochengewebe aufgespeichert wurde die Verteilung des Strontium erfolgte recht unregelmassig je nach dem Mass der Knochenbildung oder der Entartungsprozesse

## RÉSUMÉ

Dans l étude autoradiographique de la distribution du radiostrontium dans les ostéo arcomes osteogeniques le strontium 85 donne une meilleure résolution que le strontium 90 On trouve une fixation de radiostrontium beaucoup plus élevee dans la tumeur que dans l os normal sa distribution etant tres irreguliere et liée aux variations de la minéralisation et aux modifications degénératives

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FROM THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, DEPT 1, SUNDBYBERG, SWEDEN

# RADIOPROTECTIVE EFFECTS OF S PHOSPHORYLATED THIOLS

by

STIG ÅKERFELDT

It was recently reported by HANSEN & SORBO (1961) as a result of a search for new radioprotective substances at this institute that one of the S phosphorylated thiols earlier synthesized by ÅKERFELDT (1959) namely cysteamine S phosphate is a potent radioprotective agent when given to mice This fact has stimulated the synthesis of a series of related compounds (ÅKERFELDT 1962) and a preliminary investigation of their properties as potential anti radiation drugs is reported in this paper

*Methods* Male mice of an inbred CBA strain 10 to 12 weeks old and weighing 22 ± 2 g were used in this investigation Total body irradiation was delivered from a roentgen generator operated at 260 kV and 10 mA with 4 mm Al and 0 5 mm Cu filters Furthermore an irregular copper filter (average thickness 0 1 mm) was inserted to counteract differences in radiation intensity in different parts of the radiation field The animals were kept in plastic cages during irradiation The FTD was 40 cm and the dose rate 74 r min$^{-1}$ The total roentgen dose given was 1 092 r which corresponded to LD [illegible] The LD [illegible] for the mice strain used was 718 r

The compounds to be investigated were dissolved in saline adjusted to pH 7 and 0 3 ml of the solution injected intraperitoneally into 30 mice 15 min before irradiation The amount of compound injected into each animal corresponded roughly to 1 LD [illegible] An estimation of $LD_0$

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**Table 1**

*Acute toxicities and radioprotective effects of S phosphorylated thiols*

| No | Compound | $LD_{50}$ mmole per kg bodyweight | Dose mmole per kg bodyweight | 30-day survival |
|---|---|---|---|---|
| 1 | $NH_2CH_2CH_2SH$ | 4.0 | 1.75 | 93—100 |
| 2 | $NH_2CH_2CH_2SPO_3HNa$* | 5.2 | 2.2 | 95 |
| 3 | $CH_3NHCH_2CH_2SPO_3Na_2$ | >0.5 | 0.5 | 0 |
| 4 | $(CH_3)_2NCH_2CH_2SPO_3Na_2$ | 3.0 | 0.5 | 0 |
| 5 | $(CH_3)_3NCH_2CH_2SPO_3^-Na$ | 0.2 | 0.08 | 0 |
| 6 | $(i-C_3H_7)_2NCH_2CH_2SPO_3Na_2$ | 0.7 | 0.5 | 0 |
| 7 | $NH$ / $C—NHCH_2CH_2SPO_3^-(NH_4)_{0.2}Li_{0.8}$ / $NH_2$ | 1.7 | 1.4 | 97 |
| | | | 0.7 | 53 |
| 8 | $NH\ CH_2CH_2CH_2SPO_3HLi$ | >1.0 | 1.0 | 4 |
| 9 | $NH$ / $C—NH(CH_2)_3SPO_3^-(NH_4)_{0.8}Li_{0.2}$ / $NH_2$ | 1.6 | 1.0 | 80 |
| | | | 0.5 | 13 |
| 10 | $(CH_3)_2NCH_2CH(CH_3)SPO_3Li_2$ | 1.8 | 1.5 | 81 |
| | | | 0.75 | 13 |
| 11 | $NH_2COCH_2SPO_3Li_2$ | >1.0 | 1.0 | 0 |
| 12 | $HOCH_2CH_2SPO_3Li_2$ | >1.0 | 1.0 | 0 |
| 13 | $HOCH_2CH_2CH_2SPO_3Na_2$ | 1.0 | 0.5 | 0 |
| 14 | $CH_3CH_2SPO_3Li_2$ | >1.0 | 1.0 | 0 |
| 15 | $Li\ PO_3SCH_2CH(OH)CH_2SPO_3Li$ | 0.2 | 0.13 | 0 |
| 16 | $Li\ PO_3SCH_2CH(SPO_3Li_2)CH_2OH$ | 0.3 | 0.25 | 0 |

* Calculated from data by HANSEN & SORBO (1961)

and $LD_{50}$ was obtained after intraperitoneal injection of the substances (dissolved in 0.3 ml saline) into 10 to 30 mice Thirty control mice given 0.3 ml of saline and 30 mice injected with 0.3 ml of saline containing cysteamine corresponding to 1.75 millimoles per kg body weight were used in each experiment

Cysteamine S-phosphate + cysteamine in tissues after intraperitoneal injection of cysteamine S phosphate was determined in the following way The tissue was homogenized in its double volume of 10 % cold trichloro-acetic acid After centrifugation a sample of the clear supernatant was heated for 2 min at 100 and cysteamine in the solution was determined colorimetrically according to GRUNERT & PHILLIPS (1951)

The chromatographic methods used for the identification of urinary excretion products of injected cysteamine S-phosphate have been reported elsewhere (AKERFELDT 1959)

**Radioprotective effects of S-phosphorylated thiols**

The results are presented in Table 1 It is evident that of the new compounds tested three have good radioprotective properties, namely 2 guanidinoethanethiol S phosphate (compound No 7), 3 guanidinopropanethiol S phosphate (compound No 9) and 2 dimethylamino 1 methylethanethiol S phosphate (compound No 10) These three substances are good radioprotectors at concentrations below those necessary for a protective effect with cysteamine or cysteamine S phosphate but they are more toxic Reduction of the dose considerably decreases the effectiveness of the compounds Nos 9 and 10 but does not affect the protective action of compound No 7 to the same extent A concentration intermediary to those investigated for compound No 7 may therefore be sufficient for maximal protectivity of this substance

Table 1 clearly shows that substitution of R in compounds containing an unbranched carbon chain $R(CH_2)_nSPO^{=}$ (where n = 2 or 3) for hydrogen, alkylated amino groups or hydroxyl groups produces compounds that are completely ineffective as radioprotectors at the dose levels tested

Compound No 15 has the same spacing between the sulfur atoms as lipoic acid and compound No 16 is diphosphorylated British Anti Lewisite (BAL) Both are relatively toxic and have no radioprotective effects in the concentrations tested For protective effect, the substituent (R) must include an unsubstituted $NH_2$ group such as the guanidino or amino group It is noteworthy that the $NH_2$ group of the amide No 11 is devoid of protective activity This is probably due to the tautomeric properties of the amido group

The radioprotective properties of compound No 10 are surprising This is the first instance in which a substance containing an alkylated amino group has been shown to be a potent radioprotector Since the analogue with an unbranched carbon chain (No 4) is ineffective the action of compound No 10 must be associated with the presence of an $\alpha$ methyl group

*Mode of action* S phosphorylated thiols are easily hydrolyzed enzymically by a number of tissues of the animal body The products formed are ortho phosphate and a thiol (ÅKERFELDT 1960 1962) It would therefore appear that the radioprotective effect of S phosphorylated thiols is at least partly due to the enzymic formation of thiols from these compounds This conclusion is also supported by the following facts

1 Variation of the structure of the substituent and of the length of the carbon chain has the same influence on the radioprotectivity of S phosphorylated thiols as it has on that of the corresponding thiols (LANGENDORFF & KOCH 1956 SHAPIRA et coll 1957, and DOHERTY et coll 1957,

2 The guanidino derivatives Nos 7 and 9 are effective at the same dose levels as are the corresponding thiols (SHAPIRA et coll 1957) Compounds Nos 7 and 9 and the corresponding thiols are not effective when given after irradiation This was the case also with compound No 10

**Table 2**

*Concentration of cysteamine + cysteamine S phosphat (CASP) in various organs of mice 0 5 and 1 hour after intraperitoneal injection of 0 11 mmole cysteamine S phosphate in 0 3 ml saline*

| Organ | μmole SH/g tissue control animal* | μmole SH/g tissue CASP animal | | Difference between CASP and control animal μmole SH/g tissue | |
|---|---|---|---|---|---|
| | | 0 5 hour | 1 hour | 0 5 hour | 1 hour |
| Liver | 7 05 | 11 1 | 10 1 | 4 05 | 3 05 |
| Spleen | 1 23 | 3 83 | 3 12 | 2 60 | 1 89 |
| Kidney | 4 82 | 14 4 | 8 60 | 9 58 | 3 78 |

* Calculated as cysteamine

**Table 3**

*Concentration of cysteamine — cysteamine S phosphate (CASP) in various organs of rats 0 5 and 1 5 hours after intraperitoneal injection of 0 34 mmole cysteamine S phosphate in 0 6 ml saline*

| Organ | μmole SH g tissue control animal* | μmole SH/g tissue CASP animal | | Difference between CASP and control animal μmole SH/g tissue | |
|---|---|---|---|---|---|
| | | 0 5 hour | 1 5 hours | 0 5 hours | 1 5 hours |
| Liver | 5 30 | 5 94 | 7 00 | 0 64 | 1 70 |
| Kidney | 5 01 | 5 51 | 5 30 | 0 50 | 0 29 |
| Spleen | 2 86 | 3 56 | 3 14 | 0 70 | 0 28 |
| Marrow | 0 76 | 1 12 | 1 78 | 0 36 | 1 02 |

* Calculated as cysteamine

*Distribution of intraperitoneally injected cysteamine S phosphate in various organs of the mouse and rat* It was mentioned that cysteamine S phosphate and other S phosphorylated thiols are rapidly hydrolyzed by enzymes present in various organs of mammals Intraperitoneally injected cysteamine S phosphate will therefore be recovered in various tissues both as cysteamine and as unchanged cysteamine S phosphate (In addition, small amounts of other metabolites may possibly be present ) The method chosen to investigate the concentrations of the injected radioprotector in the tissues was such that it measured both cysteamine and unchanged cysteamine S phosphate The deproteinized acid tissue homogenate was therefore hydrolyzed at 100° for a few minutes, a procedure that gives a quantitative yield of cysteamine from any cysteamine S phosphate present (ÅKERFELDT 1962) This technique is superior to the one using $^{35}$S labelled compounds, since it measures only the amount of radio protector present, it does not measure the amounts of possible metabolites (which do not contain the thiol group)

Organs of mice and rats that had received 0 11 to 0 34 millimoles cysteamine S phosphate intraperitoneally were analyzed 0 5, 1 and 1 5 hours

after the injection Representative results are presented in Tables 2 and 3 and show that the radioprotector rapidly increases the amount of available thiol groups in all tissues studied These results are in agreement with earlier studies performed on cysteamine, e g by SORBO (1962), who also demon strated that the increased thiol concentration in liver and spleen could not be attributed only to the cysteamine present in the blood of these tissues

*Urinary excretion products of cysteamine S phosphate* Paper chromatographic analysis of urine collected from rats that had received intraperitoneal injection of cysteamine S phosphate was performed (a) on untreated urine (b) after coupling of the excreted thiols to 6 chloromercuri 2 nitrophenol (ÅKERFELDT 1959), and (c) after iodine oxidation of the excreted thiols

The results showed that only traces of cysteamine S phosphate remained Small amounts of cystamine were found but by far the largest portion of the cysteamine S phosphate injected had been hydrolyzed to cysteamine which was the only detectable thiol present Hypotaurine and taurine were possibly present in trace amounts

The main urinary excretion products are thus cysteamine and ortho phosphate

## Acknowledgements

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## SUMMARY

Fourteen different S phosphorylated thiols ha e been investigated as to their radioprotec tive properties in mice The distribution of intraperitoneally injected cysteamine S phosphate in certain organs of rats and mice and the urinary ex tion products of cysteamine S phosphate were al o examined

## ZUSAMMENFASSUNG

Vierzehn verschieden S phosphoryl Thiole wurden an Mausen auf ihren Schutzwert gegen radio-aktive Korp gepruft Die Verteilung von intraperitoneal injiziertem Cysteamin S phosphat in bestimmt Organen von Ratten und Mausen sowie die renal Ausscheidung von Abbauprodukten Cysteamin S phosphates wurden ebenfalls unter ucht

## RÉSUMÉ

Les propriétés ra protectrices de quatorze thiols S pho pl lés différents ont été étudiées sur la sour l auteur a aussi examiné la distribution d certains organes de rats et de souris du S ph phate de cystéamine injecté dans le p r et les produits d excrétion urinaire du S phosphate de cystéamine

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# PROTECTIVE EFFECT OF CYSTEAMINE AT FRACTIONATED IRRADIATION

## I Lethality up to 30 days after last irradiation

by

ARNE NELSON, OLA HERTZBERG and INGA BRITT HENRICSSON

A considerable amount of information is accumulating on the protective ments of numerous chemical compounds in acute injuries measured as lethality caused by single whole body irradiation (reviewed by ELDJARN & PIHL (1960), and others) Few attempts have however been made to investigate the effect of protective substances at fractional irradiation up to accumulated lethal doses or at continuous long term irradiation

PATT et coll (1953) investigated the protective effect of cysteine on mice by using a split exposure technique The interval between successive radiation fractions did not, however exceed 5 min The two fractions varied from 100 to 700 r and the amount of cysteine injected was proportional to the radiation dose PATT concluded from his results that irradiation prior to cysteine administration does not influence the protection against subsequent exposure and that the lethal potential of small dosages of radiation cannot be reversed by cysteine under these conditions

RUGH & CLUGSTON (1954) could not observe any protective effect of cyste

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amine on mice given 100 r per day The protected mice died after an average accumulated dose of 1 230 r the corresponding value for the controls being 1 440 r LANGENDORFF & CATSCH (1956) gave two doses of 175 to 500 r with 24 hour intervals and found a protective effect of cysteamine, which, however, was less than that with single doses Later LANGENDORFF et coll (1959) tested the effect of serotonin They gave three fraction doses of 505 to 1 100 r with 30 day intervals and 750 to 1 050 r with 15 day intervals and observed a good protective effect NOBLE et coll (1960) gave ten daily doses of 50 to 200 r to mice and noticed a protective effect with AET DOULL et coll (1960) in a similar investigation observed a significant reduction in the 30 day mortality with serotonin and dimethyldithiocarbamide acid, but no effect with cysteamine

The few studies on the protective effects obtained have resulted in equivocal results due to the rather limited range of fraction doses intervals and accumulated doses It is likely that an investigation with a wider range would give valuable information concerning the mechanisms of protection and of recovery, and an answer to the question whether the chemical protection is due to a dose reduction effect or to an enhanced recovery, might perhaps be obtained

The present investigation is an attempt to elucidate some of these problems

## Material and Methods

*Animals* In all experiments only male mice of an inbred CBA strain were used Their age was 60 to 70 days at the first irradiation

*Irradiation conditions* The roentgen apparatus was operated at 260 kV and 10 mA filter 0 5 mm Cu inherent filtration 4 mm Al, dose rate 84 r/min distance between the roentgen tube and the object approximately 40 cm

The animals were irradiated in groups of ten in a plastic 'wheel' and were then placed together in a cage Because of the growth of the animals during the experimental period single animals were suffocated in the radiation wheel The area of the breathing holes in the wheels was therefore increased to give the animals ample air supply, this possibly influenced the radiosensitivity This change was made between two series of experiments in August 1961, but one group (160 r, 7 days) was carried through at the changed conditions

The irradiation schedule giving fractionated doses accumulated doses, and intervals, is presented in Tables 1 to 7

Groups of animals consisting of about 60 mice were exposed under the same irradiation conditions Half the number received an intraperitoneal injection of 3 mg cysteamine 15 min before the irradiation

*Controls* In several of the untreated control groups, each consisting of 50 mice no deaths occurred during the observation time, which in some cases was extended to 11 months

**Table 1**

*Mortality after fraction dose 80 r — time interval 1 day (numbers in italics [illegible])*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals | | Distribution of deaths during observation time (days) | | | | | | Survival at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At beginning of irradiation | At end of irradiation | 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | | |
| 13.2.62 | 640 | 30 | 30 | | | | | | | 30 | |
| | *640* | *30* | *27* | | | | | *1* | | *2[illegible]* | *1* |
| | 960 | 30 | 30 | 1 | | | | | | 29 | |
| | *960* | *30* | *29* | | | | | | | *29* | *3.3* |
| | 1 280 | 30 | 30 | 2 | 2 | 2 | | | | 24 | 20.0 |
| | *1 280* | *30* | *23* | *2* | *1* | | | | | *20* | *33.3* |
| | 1 600 | 30 | 27 | 9 | 8 | 4 | 2 | | | 4 | 86.6 |
| | *1 600* | *30* | *17* | *2* | *1* | | | | *1* | *13* | *56.7* |
| | 1 920 | 30 | 15 | 13 | 1 | 1 | | | | 0 | 100.0 |
| | *1 920* | *30* | *13* | *2* | *3* | *3* | | | | *5* | *83.2* |
| 28.8.62 | 640 | 20 | 20 | | | | | | | 20 | 0 |
| | 800 | 20 | 20 | | | | | | | 20 | 0 |
| | 960 | 20 | 20 | | | 1 | | | | 19 | 5.0 |
| | 1 120 | 20 | 19 | | | | | | | 19 | 5.0 |
| | 1 280 | 20 | 20 | 4 | 1 | | | | | 15 | 25.0 |
| | 1 440 | 20 | 17 | 3 | 2 | | | | | 12 | 40.0 |
| | 1 600 | 20 | 11 | 5 | | | | | | 6 | 70.0 |
| | 1 760 | 20 | 8 | 4 | 3 | | | | | 1 | 95.0 |

The toxicity of cysteamine was tested in some non irradiated groups. Of 50 mice receiving cysteamine every day for 24 days, 48 survived and out of 49 mice injected once a week for more than 40 weeks 46 survived.

A mathematical model (see below) based on the results of the first series in 1960—1961 was designed and used for an extended examination in 1961—1962. Complementary experiments were carried out during the autumn of 1962 in order to obtain further confirmation of the applicability of the mathematical model.

The mortality in the early series was observed up to only 30 days after the last irradiation. The observation in the later series was extended to the life span of the animals. Only the 30 day mortality is reported in this paper, however.

## Results

The results of the experiments are presented in Tables 1 to 7, they are reported upon in groups defined by a certain fraction dose at a given interval

**Table 2**

*Mortality after fraction dose 160 r — time interval 1 day (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals | | Distribution of deaths during observation time (days) | | | | | | Survivals at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At beginning of irradiation | At end of irradiation | 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | | |
| 17.1.62 | 480 | 30 | 30 | | | | | | | 30 | 0 |
| | *480* | *30* | *30* | | | | | | | *30* | *0* |
| | 800 | 30 | 30 | | 3 | 3 | | | | 24 | 20.0 |
| | *800* | *30* | *30* | | *1* | | | | | *29* | *3.3* |
| | 1 120 | 30 | 30 | | 24 | 4 | | | | 2 | 93.2 |
| | *1 120* | *30* | *30* | | *13* | *3* | | | | *14* | *53.3* |
| | 1 440 | 30 | 30 | 6 | 24 | | | | | 0 | 100.0 |
| | *1 440* | *30* | *29* | *6* | *23* | | | | | *0* | *100.0* |
| | 1 760 | 30 | 30 | 26 | 4 | | | | | 0 | 100.0 |
| | *1 760* | *30* | *22* | *19* | *3* | | | | | *0* | *100.0* |
| 28.8.62 | 480 | 20 | 20 | | | | | | | 20 | 0 |
| | 800 | 20 | 20 | | | | | | | 20 | 0 |
| | 1 120 | 20 | 20 | | 15 | 2 | | | | 6 | 70.0 |
| | 1 440 | 20 | 20 | 5 | 13 | 2 | | | | 0 | 100.0 |

1. *Fraction dose 80 r, interval 1 day* (Table 1). No conclusions can be drawn regarding any protective effect against radiation from the series in which cysteamine has been tested. It is, however, apparent that the protected animals which survived the treatment period showed a lower mortality during the observation time than those that were unprotected. The accumulative toxic effect of the substance must also be taken into consideration. It was often noted during this experimental series that the death of animals occurred in close connection with injection of cysteamine or with irradiation. This phenomenon will form the subject of a special investigation.

2. *Fraction dose 80 r, interval 3 days*. In accordance with the mathematical model, no acute death occurred in this series. The results will therefore be reported in a paper on chronic effects.

3. *Fraction dose 160 r, interval 1 day* (Table 2). In spite of the daily repeated irradiations, only a few unprotected animals could not tolerate higher accumulated doses, but the number of survivals was significantly higher compared with the number unprotected. Because of the relatively low number of cysteamine injections no accumulated toxic effect was observed.

4. *Fraction dose 160 r, interval 3 days* (Table 3). All animals survived after 960 r but some unprotected mice died after 1 280 r. The mortality increased con

**Table 3**

*Mortality after fraction dose 160 r — time interval 3 days (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals | | Distribution of deaths during observation time (days) | | | | | | Survivals at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At beginning of irradiation | At end of irradiation | 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | | |
| 7 11 60 | 960 | 30 | 30 | | | | | | | 30 | 0 |
| | *960* | *30* | *30* | | | | | | | *30* | *0* |
| | 1 280 | 30 | 30 | | 1 | 2 | | | | 27 | 10 0 |
| | *1 280* | *30* | *29* | | | | | | | *29* | *3.3* |
| | 1 600 | 30 | 29 | 2 | 3 | 7 | 4 | 1 | | 12 | 60 0 |
| | *1 600* | *30* | *30* | | | | | | | *30* | *0* |
| | 1 920 | 35 | 27 | 17 | 4 | 1 | | | | 5 | 85 7 |
| | *1 920* | *35* | *35* | | | | | | | *0* | *0* |
| 22 8 61 | 1 600 | 30 | 29 | 9 | 7 | 2 | | | | 11 | 63 4 |
| | *1 600* | *30* | *29* | *2* | *2* | *3* | *2* | | *1* | 19 | *36 7* |
| | 1 920 | 29 | 23 | 13 | 6 | 3 | | | | 1 | 96 5 |
| | *1 920* | *30* | *29* | *3* | *6* | *4* | | | *1* | *15* | *50 0* |
| | 2 240 | 30 | 6 | 5 | 1 | | | | | 0 | 100 0 |
| | *2 240* | *30* | *24* | *1* | *4* | *1* | | | | *18* | *40.0* |
| | 2 560 | 30 | 2 | 1 | 1 | | | | | 0 | 100 0 |
| | *2 560* | *30* | *12* | *4* | *3* | | | | | *5* | *83.3* |
| | 2 8 0 | 30 | 0 | | | | | | | 0 | 100 0 |
| | *2 880* | *30* | *3* | *2* | *1* | | | | | *0* | *100 0* |
| | 3 200 | 30 | 0 | | | | | | | 0 | 100 0 |
| | *3 200* | *30* | *1* | *1* | | | | | | *0* | *100 0* |
| | 3 520 | 30 | 0 | | | | | | | 0 | 100 0 |
| | *3 5 0* | *30* | *2* | *1* | | | | | | *1* | *96 7* |
| 28 8 62 | 960 | 20 | 20 | | | | | | | 20 | 0 |
| | 1 280 | 20 | 20 | | | | | | | 20 | 0 |
| | 1 600 | 20 | 20 | | | | 1 | | | 19 | 5 0 |
| | 1 920 | 20 | 15 | 8 | 3 | 2 | | | | 2 | 90 0 |
| | 2 240 | 20 | 13 | 6 | | | 2 | | 1 | 4 | 80 0 |

siderably after 1 600 r and after 2 240 r all the animals died The protective effect of cysteamine is apparent the protected mice did not begin to die until after 1 600 r and some survived even after 2 560 r

5 *Fraction dose 160 r interval 7 days* (Table 4) All the irradiated unprotected mice survived an accumulated dose of 2 240 r After 3 200 r about 50 % of the animals survived but in the dose range of 3 840 r to 4 800 r only a few mice survived All animals died after 5 760 r A significant increase in the number

**Table 4**

*Mortality after fraction dose 160 r — time interval 7 days (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals: At beginning of irradiation | Number of animals: At end of irradiation | Distribution of deaths during observation time (days): 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | Survivals at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 19 8 60 | 1 280 | 30 | 30 | | | | | | | 30 | 0 |
| | *1 280* | *30* | *30* | | | | | | | *30* | *0* |
| | 1 600 | 30 | 30 | | | | | | | 30 | 0 |
| | *1 600* | *30* | *30* | | | | | | | *30* | *0* |
| | 1 920 | 30 | 30 | | | | | | | 30 | 0 |
| | *1 920* | *30* | *30* | | | | | | | *30* | *0* |
| | 2 240 | 35 | 35 | | | | | | | 35 | 0 |
| | *2 240* | *35* | *35* | | | | | | | *35* | *0* |
| 17 5 61 | 2 880 | 28 | 23 | | 1 | | 2 | 2 | | 18 | 35 7 |
| | *2 880* | *27* | *25* | | | | | | | *25* | *7 4* |
| | 3 200 | 29 | 27 | 1 | 6 | 1 | 2 | 1 | 1 | 15 | 48 3 |
| | *3 200* | *29* | *21* | *2* | | *1* | *2* | *1* | | *15* | *48 3* |
| | 3 520 | 29 | 15 | 1 | | 2 | | | | 12 | 58 6 |
| | *3 520* | *29* | *28* | | | | | *1* | | *27* | *6 9* |
| | 3 840 | 28 | 5 | | 1 | 1 | | 1 | 1 | 1 | 96 5 |
| | *3 840* | *28* | *14* | | *2* | | | *1* | *1* | *10* | *64 3* |
| | 4 160 | 28 | 8 | 4 | 2 | 1 | | | | 1 | 96 5 |
| | *4 160* | *21* | *5* | | | | | | *1* | *4* | *81 0* |
| | 4 480 | 27 | 4 | | | | 1 | | 1 | 3 | 97 5 |
| | *4 480* | *30* | *17* | *1* | *1* | | | *2* | | *13* | *56 7* |
| | 4 800 | 28 | 2 | | 1 | | | | | 1 | 96 5 |
| | *4 800* | *29* | *14* | | *3* | *1* | *1* | | | *8* | *72 3* |
| | 5 760* | 28 | 1 | 1 | | | | | | 0 | 100 0 |
| | 5 920** | 27 | 1 | 1 | | | | | | 0 | 100 0 |

* This group should have been irradiated 40 times The last mouse died on the day following the 30th irradiation

** This group should have been irradiated 40 times The last mouse died on the 5th day following the 37th irradiation

of survivors was observed among the protected groups in the dose range of between 3 520 r and 4 800 r, in comparison with the unprotected groups All the mice were dead after 5 920 r, however

6 *Fraction dose 320 r, interval 1 day* (Table 5) All unprotected animals survived an accumulated dose of 640 r, but already at 960 r the majority had died, and all were dead after 1 280 r A few protected mice died at 960 r, at 1 280 r some survived, and at 1 600 r all died

**Table 5**

*Mortality after fraction dose 320 r — time interval 1 day (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals: At beginning of irradiation | At end of irradiation | Distribution of deaths during observation time (days): 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | Survivals at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 6 6? | 640 | 30 | 30 | | | | | | | 30 | 0 |
| | *640* | *30* | *30* | | *1* | | | | | *29* | *3.3* |
| | 960 | 30 | 30 | 4 | 7 | 9 | | 1 | | 9 | 70 0 |
| | *9?0* | *30* | *29* | *1* | | | | | | *?8* | *6 7* |
| | 1 280 | 30 | 30 | 1 | 28 | 1 | | | | 0 | 100 0 |
| | *1 ?80* | *30* | *29* | | *12* | *9* | *1* | | | *7* | *76.8* |
| | 1 600 | 35 | 32 | 5 | 27 | | | | | 0 | 100 0 |
| | *1 600* | *35* | *24* | *3* | *?0* | *1* | | | | *0* | *100 0* |

7 *Fraction dose 320 r interval 3 days* (Table 6) Some unprotected mice died already at an accumulated dose of 960 r and the mortality was 100 % at doses higher than 1 280 r Some of the protected animals died after 1 280 r but some survived at 1 920 r indicating a good protection also in this case

8 *Fraction dose 320 r, interval 7 days* (Table 7) A few deaths are recorded among the irradiated animals only at accumulated doses of 1 280 r and 1 600 r but at 1 920 and 2 240 r only a few survived A very low mortality in the protected animals is however, evident in this dose range and at 3 200 r some survivors still remain The protective effect of cysteamine in this group is obvious

## Mathematical model and Statistical analysis

According to the general opinion the r very rate decreas s in the time intervals between irradiations This implies that the reco ery rate during th fi t 24 h ur after an irradiation should be greater than the recov y rate d ring the follo w da Furtherm re the recovery rate is considered to be depen t o a p evious irradiat i e B AIR 1961 SACHER 1958 STORER 1961)

Systematic deviations in i t ng that a impler mod l ld c ver e ident when these concepts were applied to t p r sent lt A mathemati l m d l was th refore designed on the assumption that th al olt y was indep t of an p r us dose and independent of the time nt r al b t th ied ately pre i irrad ati The recovery rate per dav was assum l t t t ch animal The eff ctive dose received by an animal is then

$$ERD = AED - R \cdot T$$

where AED is the accumulat l exposure l R the recovery rat in r/day and T is the number of recovery days i e th tim p eriod betw r th e first and last irradiation (Fig 1) If $R \cdot T \geq$ AED ERD is defined as 0

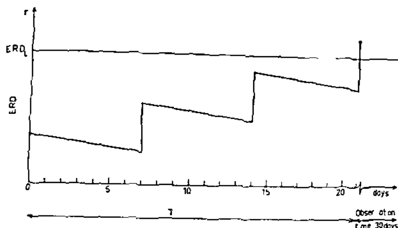



Fig 1 ERD in r as a function of recovery time (T) for an animal whose $ERD_L$ is exceeded in the last irradiation

**Table 6**

*Mortality after fraction dose 320 r — time interval 3 days (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals: At beginning of irradiation | Number of animals: At end of irradiation | Distribution of deaths during observation time (days): 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | Survivals at end of observation time | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 7 60 | 960 | 30 | 30 | | 6 | 3 | | | | 21 | 30.0 |
| | *960* | *30* | *30* | | | | | | | *30* | *0.0* |
| | 1 180 | 30 | 30 | 13 | 13 | 2 | 1 | | 1 | 0 | 100.0 |
| | *1 280* | *30* | *30* | | *2* | *2* | *1* | | | *25* | *16.7* |
| | 1 600 | 30 | 30 | 33 | 7 | | | | | 0 | 100.0 |
| | *1 600* | *30* | *30* | *7* | *9* | *3* | *1* | | | *10* | *66.7* |
| | 1 920 | 35 | 19 | 19 | | | | | | 0 | 100.0 |
| | *1 920* | *34* | *33* | *13* | *13* | *3* | | | | *4* | *88.3* |
| 7 4 61 | 960 | 30 | 30 | | 2 | 5 | | | | 23 | 23.3 |
| | *960* | *30* | *30* | | | | | | | *30* | *0.0* |
| | 1 280 | 30 | 30 | | 24 | 2 | 3 | | | 1 | 96.6 |
| | *1 280* | *30* | *30* | | *3* | | *1* | *2* | *1* | *23* | *23.3* |
| | 1 600 | 30 | 28 | 27 | 1 | | | | | 0 | 100.0 |
| | *1 600* | *30* | *30* | *12* | *10* | *1* | | | *1* | *6* | *80.0* |
| | 1 920 | 30 | 9 | 9 | | | | | | 0 | 100.0 |
| | *1 920* | *20* | *11* | *5* | *6* | | | | | *0* | *100.0* |
| | 2 240 | 30 | 3 | 3 | | | | | | 0 | 100.0 |
| | *2 240* | *20* | *10* | *5* | *4* | *1* | | | | *0* | *100.0* |
| | 2 560 | 30 | 0 | | | | | | | 0 | 100.0 |
| | *2 560* | *29* | *2* | *2* | | | | | | *0* | *100.0* |

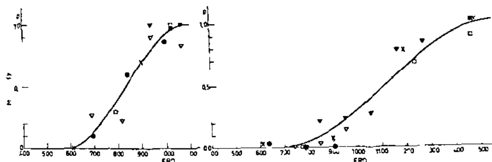



Fig 2 Mortality as a function of ERD (series I) a) irradiated only b) irradiated and protected.

- ● 160 r 3 days started 7 11 1960
- × 320 r 1 day » 13 6 1960
- □ 320 r 3 days » 5 7 1960
- ■ 320 r 3 days » 7 4 1961
- ▽ 320 r 7 days » 22 9 1960
- ▼ 320 r 7 days » 7 2 1961

**Table 7**

*Mortality after fraction dose 320 r — time interval 7 days (numbers in italics indicate protected groups)*

| Series started | Accumulated exposure dose (AED) (r) | Number of animals | | Distribution of deaths during observation time (days) | | | | | | Survivals at end of observation time | Mortality % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | At beginning of irradiation | At end of irradiation | 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | | |
| 22 9 60 | 1 280 | 30 | 30 | | | 4 | 2 | 2 | | 22 | 26 7 |
| | *1 280* | *30* | *30* | | | | | | | *30* | *0 0* |
| | 1 600 | 30 | 30 | 1 | | 3 | | 2 | 1 | 23 | 23 4 |
| | *1 600* | *30* | *30* | | | | | | | *30* | *0 0* |
| | 1 920 | 30 | 27 | 10 | 10 | 4 | | | | 3 | 90 0 |
| | *1 920* | *30* | *29* | | | | | | | *29* | *3.3* |
| | 2 240 | 35 | 26 | 13 | 5 | 1 | 1 | | | 6 | 82.8 |
| | *2 240* | *35* | *35* | | *2* | *2* | *1* | | | *30* | *14.3* |
| 7 2 61 | 1 920 | 30 | 15 | 14 | 1 | | | | | 0 | 100 0 |
| | *1 920* | *28* | *27* | *1* | | | *2* | *1* | *1* | *22* | *21 4* |
| | 2 240 | 30 | 1 | 1 | | | | | | 0 | 100 0 |
| | *2 240* | *30* | *27* | *4* | | | | | | *23* | *23 4* |
| | 2 560 | 29 | 29 | | | | | | | 0 | 100 0 |
| | *2 560* | *30* | *24* | *2* | | | | | | *2[illegible]* | *26.[illegible]* |
| | 2 880 | 30 | 30 | | | | | | | 0 | 100 0 |
| | *880* | *30* | *10* | *1* | | *1* | | | *1* | *7* | *76.6* |
| | 3 200 | 30 | 30 | | | | | | | 0 | 100 0 |
| | *3 200* | *30* | *6* | | | *1* | | | | *5* | *83 4* |

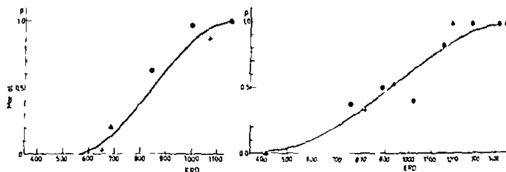



Fig. 3. Mortality as a function of ERD (series II) a) irradiated only b) irradiated and protected

| | | | |
|---|---|---|---|
| + | 80 r 1 day | started | [illegible] |
| ▲ | 160 r 1 day | | [illegible] |
| ● | 160 r 3 days | » | [illegible] |

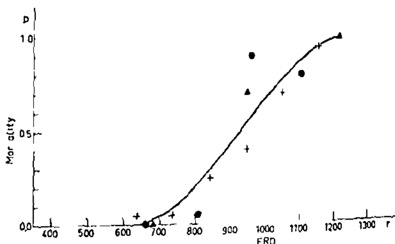



Fig. 4. Mortality as a function of ERD ([illegible] III) irradiated only

| | | | |
|---|---|---|---|
| + | 80 r 1 day | started | 28 8 1962 |
| ▲ | 160 r 1 day | | 28 8 1962 |
| ● | 160 r 3 days | | 28 8 1962 |

ERD is thus the accumulated dose corrected for such recovery as has occurred at a specific time (T).

If during the irradiation period the dose received by an animal exceeds a certain value $ERD_L$ death occurs according to the model before the end of the observation time i.e. within 30 days after the last irradiation. It appears from Fig. [illegible] that if $ERD_L$ is not exceeded at the last irradiation the animal will survive.

The relationship between mortality and dose in our animal material may be expressed as a sine square distribution and this has therefore been assumed in our model for the distribution of $ERD_L$. The relation between mortality and ERD will form an S shaped curve which will only differ slightly from the normal distribution. When the sine square distribution is applied the observed mortality rate $p$ is transformed according to

$$y = 2 \arcsin \sqrt{p} \text{ in which case}$$

$$y = a + b\,(\text{ERD}) \quad (a \text{ and } b \text{ are constants})$$

After substitution of ERD

$$y = a + b\,(\text{AED} - \text{R}\ \text{T}) = a + b\,(\text{AED}) - c\ \text{T where } c = b\ \text{R}$$

The variable $y$ can accept values between 0 and $\pi$

By means of regression analysis $a$ $b$ and $c$ can be estimated in which case an estimation of $\text{R} = \frac{c}{b}$ can be obtained

The statistical analysis gave the following equations for the five regression planes

| | | | |
|---|---|---|---|
| Ser I | Ir | $y = -3\,39 + 0\,005979\ (\text{AED}) - 0\,1651\ \text{T}$ | $\text{R} = 28$ |
| Ser I | Ir + P | $y = -2\,39 + 0\,003536\ (\text{AED}) - 0\,1086\ \text{T}$ | $\text{R} = 31$ |
| Ser II | Ir | $y = -2\,80 + 0\,005148\ (\text{AED}) - 0\,1435\ \text{T}$ | $\text{R} = 28$ |
| Ser II | Ir + P | $y = -1\,06 + 0\,002876\ (\text{AED}) - 0\,0901\ \text{T}$ | $\text{R} = 31$ |
| Ser III | Ir | $y = -3\,15 + 0\,005098\ (\text{AED}) - 0\,1496\ \text{T}$ | $\text{R} = 29$ |

(Ir = irradiated P = protected)

Series I includes experimental groups started not later than April 4th 1961 series II was started between August 22nd 1961 and February 13th 1962 while series III was started on 28th of August 1962

Thus $y$ is the expected value of $y$ according to the model From $y$ the expected mortality can be calculated which for $0 \leq \hat{y} \leq \pi$ is $0 \leq p \leq 1$

$y < 0$ is regarded as $p = 0$ and $y > \pi$ as $p = 1$

The estimations of ERD can be obtained for each group of animals from AED T and the estimation of R

The curves in Figs 2 3 and 4 give the relation between $p$ and ERD The observed mortality rates are marked in the figures

The curves *for Ir + P are extended over a greater range of* ERD *than the curves for Ir only* e g the standard deviation of $\text{ERD}_\text{L}$ is greater for the protected than for the unprotected animals The mean square deviation of the observed values around the function that indicates the relationship between dose and mortality should not be significantly greater than the theoretical variance determined by the binomial distribution The mean square deviation around the lines in Figs 2 3 and 4 is however significantly greater than the theoretical variance This might depend on those age differences that arise due to the long duration of the experiment even if the animals were of the same age at its inauguration In addition it should be pointed out that the various groups in series I and II were investigated at different times

The most important control investigation of the validity of the model is an observation of systematic deviations e g if points based on the same experimental conditions in Figs 2 3 and 4 tend to show a systematic shift in relation to the curves It is evid nt from Fig 2a that some points show a deviation from the curve which is great in compar on ith the expected deviation defined by the binomial distribut on althou h a systemat d viation is not observed in any group Neither in Fig 2b where protection has been added can any systematic deviation be observed

A systematic deviation is noted in Figs 3 and 4 which could indicate a higher recovery rate after a low dose e g the points of the 80 r and 1 day group how a lower mortality than might be expected There is how e r no reason t conclude from the result that the re overy rate for the 160 r and 1 day group should b gr ater than the recovery rate for the 160 r and 3 day group

## Conclusions

The *mathematical model was designed as a means of providing a statistical* analysis of the acute lethal effect of fractionated irradiation In the case of sufficiently low fraction dose or long enough interval i e within 30 days after

the last irradiation, no acute mortality is observed When the duration of the experimental period is very extended, chronic effects will influence the results and a systematic deviation from the model is introduced, e g in the 160 r and 7 day groups Such a systematic deviation has, however, not been observed within 90 days from the first irradiation in the present study No conclusion can be drawn regarding the validity of the model at shorter times since no experiment has been carried out with intervals shorter than 24 hours between the fraction doses

The good agreement between the recovery rates of the irradiated as well as of the irradiated protected groups both in series I and II, in spite of the fact that the experiments were carried out at different times, is of great interest Somewhat higher recovery rates have certainly been observed among the animal groups that received cysteamine but the difference must be regarded as insignificant

The protective influence of cysteamine is apparent and the recovery rates are practically the same in the protected and unprotected groups which further supports the opinion that the results produced by cysteamine [illegible] initial, i e dose reduction effects

**Acknowledgement**

The authors are indebted to C Ronnback S Jager I Andersson and R von Knorring for their excellent technical assistance

## SUMMARY

Groups of mice were exposed to fraction doses at various time intervals in order to investigate the protective effect of cysteamine at sublethal levels of irradiation Half the number of animals were given cysteamine before each irradiation A simple mathematical model which fitted the results regarding the short term lethal effects was used Cysteamine appears to act by producing a dose reduction effect and not an enhancement of the recovery

## ZUSAMMENFASSUNG

Gruppen von Mausen wurden fraktionell bei verschiedenen Zeitabstanden bestrahlt um den Schutzeffekt von Cysteamin von nicht todlichen Strahlendosen zu beurteilen Die Halfte der Tiere erhielten Cysteamin vor jeder Bestrahlung Ein einfaches mathematisches Modell wurde benutzt das die Resultate der rasch todlichen Effekte darstellte Cysteamin schein mehr eine Reduktion der Strahlendose zu bewirken als die Erholung von einer Strahlendose zu begunstigen

## RESUMÉ

Des groupes de souris ont eté exposés a des doses fractionnees a intervalles de temps variés pour étudier l effet protecteur de la cystéamine pour des taux d irradiation subléthaux La moitié de ces animaux ont reçu de la cystéamine avant chaque irradiation Les auteurs se sont servis d un modele mathematique simple qui concordait avec les résultats concernant l effet léthal a court terme La cystéamine semble agir par un effet de réduction de dose et non en favorisant la guérison

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# STRAHLENSCHUTZ UND DEKONTAMINATION IN ISOTOPENLABORATORIEN

von

ULRICH O. SCHANZE

Die ständig weitergehende Anwendung von offenen radioaktiven Isotopen in allen Naturwissenschaften, in Medizin und Technik erfordert eine umfangreiche Beachtung der Schädigungsmöglichkeiten durch radioaktives Material. Wenn auch die grundsätzlichen Vorsichtsmaßregeln und Hilfsmittel zur Verhinderung einer Kontamination bekannt sein dürften und in vielen Veröffentlichungen niedergelegt sind, erscheint es dennoch ratsam, auf diesbezüglich spezielle Probleme des Strahlenschutzes hier einzugehen. Dazu gehören eine Anleitung zum Vorgehen nach Unfällen mit radioaktiver Substanz nebst Hinweisen zur Dekontamination, Empfehlungen für die Behandlung radioaktiv kontaminierter Wäsche und eine Übersicht über Arten und Verwendung von Strahlungsmonitoren im Radioisotopen-Labor.

*Verhalten bei Unfällen mit offener radioaktiver Substanz und Hinweise zur Dekontamination.* Selbst beim vorsichtigen Arbeiten sind gelegentliche, meist nur kleine Unfälle nicht zu vermeiden. Radioaktives Material, welches dabei auf die Haut oder die Kleider kommt, kann leicht inkorporiert werden, wie auf Tischen

Bei der Redaktion am 13. November 1962 eingegangen

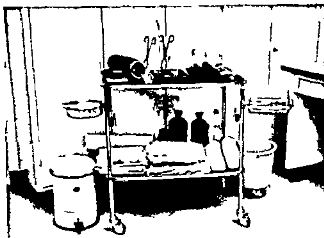


Bild 1 Strahlenschutzwagen einsatzfahig gepackt

Fußboden Handen usw gelangte Radioisotope auch bald uber Kleider und Hande den Weg in den Korper finden konnen

Bei einem Zwischenfall mit offener radioaktiver Substanz kann es sich um Aktivitaten von einigen $\mu$C als auch um mC Mengen handeln welche durch ungluckliche Umstande und/oder durch Ungeschicklichkeit verschuttet wur den Dann ist schnelles Handeln geboten, um zu verhindern daß sich radio aktive Flussigkeit durch die Kleider saugt oder pulverisierte radioaktive Substanz verstaubt und so auf die Haut oder in die Atemwege gelangt und daß die kontaminierte Aera weiter ausgebreitet wird Dann muß moglichst sofort mit der Reinigung und der Dekontamination begonnen werden Auch ist darauf zu achten daß die betreffende Person die nun einmal eingetretene Verseuchung nicht weiter verschleppt was etwa beim ubereilten Aufsuchen des Waschraumes oder auch aus anderen Grunden der Fall sein kann

Es hat sich als zweckmaßig und sehr vorteilhaft erwiesen daß alle zur Dekontaminierung und zur Überwachung derselben benotigten Dinge nicht erst jeweilig zusammengetragen werden mussen sondern an einer Stelle stets greifbar sind Der hier beschriebene Strahlenschutzwagen (Bild 1) enthalt alle diese Dinge ubersichtlich geordnet (MALLARD 1956) Er soll im Laboratoriums trakt jedoch nicht in einem Heißlabor Meßraum oder Isotopenlager selbst an gut zuganglicher Stelle stehen — etwa im Flur — und kann im Bedarfsfalle durch ein oder zwei Personen die nicht in die Kontamination verwickelt sind zum Unfallort gebracht werden Der Wagen selbst ist ahnlich den in der arztlichen Praxis verwendeten fahrbaren Instrumenten Tischchen aus Stahl rohrkonstruktion mit zwei Etagen Er soll nicht zu kleine Rader besitzen Die Bestuckung des Strahlenschutzwagens kann in drei Gruppen eingeteilt werden namlich

Monitoren (Strahlenschutzmeßgeräte)
Schutzkleidung und Schutzstoffe
Materialien und Hilfsmittel zur Dekontamination
welche im folgenden einzeln beschrieben und mit Hinweisen versehen sind

*Monitoren*

1 *Strahlenmonitor mit Ionisationskammer* empfindlich fur β und γ Strahlen geeicht in mr/h batteriebetrieben Zur Kontrolle des Strahlungsspiegels als Dosisleistung sehr praktisch in Pistolenform
2 *Strahlenmonitor mit Zahlrohr* empfindlich fur β und γ Strahlen wenn erforderlich auch fur α Strahlen mit sehr dünnem Endfenster oder Szintillationssonde netz oder batterie betrieben geeicht in Impulse/Minute Zur Kontrolle des Strahlungsspiegels und von Kontaminationen als Impulsrate Auswechselbare Zahlrohr wunschenswert genugend lange Zahlrohr und Netzkabel erforderlich
3 *Zwei Stück Taschendosimeter* Meßbereich 0 2 r hochstens 1 r Zur personlichen Dosiskontrolle wahrend des Unfalles als Extramessung Diese Dosimeter müssen sich immer im geladenen Zustand befinden

*Schutzkleidung und Schutzstoffe*

4 *Zwei Stuck Schutzkleider (Kittelform)* oder weit ubergreifend Schurzen lang aus Plastik in zwei verschiedenen Großen
5 *Zwei Paar Gummihandschuhe normal* in zwei verschiedenen Großen fertig mit Talkum zum Hineinschlupfen versehen
6 *Zwei Paar Gummihandschuhe dick mit kurzen Stulpen* in zwei verschiedenen Größen fertig mit Talkum zum Hineinschlüpfen versehen
7 *Zwei Paar Gummiuberschuhe* in zwei verschiedenen Größen
8 *Zwei Stuck lange Greifzangen* mit zwei verschiedenen Greifkopfen etwa Harwell Typ oder gleichwertige andere Typen am besten mit Pistolengriff
9 *Zwei Stück langere Tiegelzangen* vernickelt oder Edelstahl in einem Standglas
10 *Behalter fur radioaktive Abfalle* mit leicht zu öffnendem Deckel und auswechselbarem Einsatz aus Kunststoff (Wird außen am Strahlenschutzwagen angehangt)
11 *Drei Stück flache Schalen verschiedener Größe* zum Ablegen kontaminierter Gegenstande und Werkzeuge
12 *Zwei Stuck PVC Decken* etwa 1 × 2 m zum vorlaufigen Abdecken kontaminierter Gebiete oder ahnlichen Verwendungszwecken
13 *Zwei Stuck Gasmasken* siehe Text

*Materialien und Hilfsmittel zur Dekontamination*

14 *Zellstoff in Bogen* zum Abwischen
15 *Saugfahiges Lackpapier in Bogen* zum ersten Aufnehmen verseuchter Gebiete (Fußboden)
16 *Kunststoff Abziehlack und Pinsel* zum Bedecken von radioaktiv verseuchten Oberflächen
17 *Kreide* zum Bezeichnen von Kontaminationsgebieten
18 *Drei bis funf liter flussige Seife* zur Dekontamination
19 *Ein liter Kaliumpermanganatlosung* zur Hautentseuchung
20 *Ein bis zwei liter Kaliumbisulfitlösung* 5 [illegible] zum Gebrauch nach Benutzung von Kaliumpermanganatlösung
21 *Kunststoffbeutel* mit Reißverschluß zum Aufbewahren kontaminierter Kleidungsstucke
22 *Je ein bis zwei liter Tragerlösungen* der jeweils verwendeten Radioisotope (Fur ein medizinisches Isotopenlaboratorium etwa Jod und Phosphortragerlösung) Siehe Text

23. *100 ml Natriumperchloratlösung (1,2 g auf 90 ml) in graduiertem Fläschchen.* Nur notwendig, wenn mit Radiojod gearbeitet wird. Siehe Text.
24. *Ein liter Natriumthiosulfatlösung gesättigt.* Siehe Text.
25. *Langstieliger Mop zum Aufwischen,* nicht mit Holzstiel. (Mit 2 Schellen außen am Strahlenschutzwagen angeklemmt.)
26. *Kunststoffeimer* zum Aufwischen und Eintauchen des Mops. (Hängt in einem Ring außen am Strahlenschutzwagen unter dem Mop.)

Diese Aufstellung ist sowohl ausführlich durchdacht als auch in jahrelangem Einsatz praktisch erprobt, erhebt jedoch keinen Anspruch auf Vollständigkeit. Deshalb sind Abänderungen für spezielle Zwecke nicht nur möglich, sondern oftmals sogar nötig. Auch kann die hier beschriebene Grundausrüstung beliebig erweitert werden. (So empfiehlt z. B. MALLARD (1956) noch je einen Satz der wichtigsten Frauen- und Männerkleidungsstücke.)

Bei einem Unfall mit radioaktiven Substanzen müssen vor allem die betroffenen und helfenden Personen Ruhe und Besonnenheit bewahren, und gerade bei solchen Zwischenfällen zeigt sich die Wichtigkeit einer guten Ausbildung über den Umgang und die Wirkung mit und von Radioisotopen.

Der Strahlenschutzwagen wird zum Unfallort gebracht, jedoch nur so nahe an das Verseuchungszentrum heran, daß der Wagen selbst keiner Kontamination ausgesetzt ist. Der oder die Helfenden legen Schutzkleider, Gummihandschuhe (Normalausführung; die dicken mit kurzen Stulpen dienen vor allem als zusätzlicher Handeschutz bei mitunter notwendigem Hineingreifen in radioaktives Material), und Gummiüberschuhe an, dazu Taschendosimeter. Letztere dienen zur gesonderten Ermittlung der Personendosis während aller Arbeiten am Unfallort. Anschließend gilt das Hauptaugenmerk der von der Kontamination betroffenen Person, welche an eine Stelle niedrigen Strahlungsspiegels gebracht werden soll, jedoch ohne dabei Radioaktivität zu verschleppen. Der Helfende benutzt dabei den batteriebetriebenen Ionisationskammer-Monitor zur Feststellung der jeweils herrschenden Dosisleistung. Es ist zur Vereinfachung und zur Beschleunigung der Hilfsarbeiten günstig, wenn zwei Personen hierzu zur Verfügung stehen. Eine übernimmt dann die mehr aktiven Handlungen im direkten Kontakt mit der Kontamination, die andere die mehr „passiven" Tätigkeiten wie Handhabung der Monitoren und Zureichen.

Wenn es offensichtlich ist, daß die Haut auch kontaminiert oder gar das Gesicht mit radioaktiver Substanz *in Berührung kam*, *dann soll* unverzüglich an der nächsten Wasserleitung die betroffene Stelle mit viel Wasser abgewaschen werden. Kleider, die radioaktiv getränkt oder bestaubt wurden, sind sofort abzulegen und in dem Kunststoffbeutel bis zur Dekontamination aufzubewahren. Auch hierbei spielt die richtige Anwendung der Monitoren eine große Rolle. Betroffene Hautstellen sind nach dem Abwaschen mit Wasser sofort mit in flüssige Seife getauchten Zellstofflappen, die zweckmäßigerweise in einer Tiegelzange gehalten werden, zu behandeln und wieder mit Wasser abzuwaschen. Reicht dies nach kurzer Zeit nicht aus, so sind Zellstofflappen in

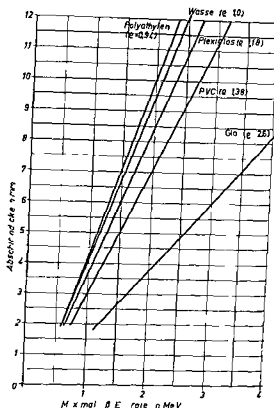



Bild 2 Dicke verschiedener Stoffe die zur volligen Abschirmung der $\beta$ Strahlen notig ist in Abhangigkeit von der maximalen Betaenergie — Abschirmdicken fur andere als in dem Bild angegebenen Stoffe konnen abgeschatzt werden da sie etwa der Dichte des Stoffes umgekehrt proportional sind

Tragerlosung (Tragerlosungen sind inaktive Formen der verwendeten radioaktiven Verbindungen) getaucht zu benutzen Letztere Methode ist meistens erfolgreich wenn aber doch noch eine Hautkontamination nachweisbar ist (Zahlrohrmonitor), muß etwa 1 Minute mit Kaliumpermanganatlosung gewaschen werden und danach mit der Natriumbisulfitlosung, welche die hautschadigende Wirkung des Kaliumpermanganats kompensiert Auch bietet die pharmazeutisch chemische Industrie Haut dekontaminierende Waschmittel an, die auch verwendet werden konnen

Ubertriebenes Reiben der betroffenen Hautstellen ist unbedingt zu vermeiden, um nicht durch Zerkratzen oder Aufrauhen der Haut eine *Ingestion* radioaktiven Materials ins Blut zu ermoglichen Jedenfalls *sollte zunachst* eine Reduktion der $\beta$ und $\gamma$ Impulsrate uber den betroffenen Stellen von unter 1 000 Imp/min erreicht werden (Endfensterzahlrohr hierzu benutzen, und vergleiche Tabelle 2 fur die endgultigen Werte)

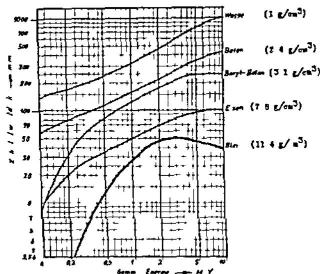



Abb 3 Zehntelwertschichten verschiedener Strahlenschutz absorber

Es muß darauf hingewiesen werden daß größere Hautverseuchungen besonders an empfindlichen Stellen, wie Gesicht und Leib wohl niemals beim Tragen der richtigen Schutzkleidung und Beachten der nötigen Vorsichtsmaßregeln (siehe Literaturverzeichnis) auftreten

Handelt es sich bei dem verschütteten Radioisotop um $^{131}J$ so ist es empfehlenswert der betreffenden Person eine Dosis von 200 mg Natriumperchlorat pro 6 Stunden zu verabreichen Das sind 15 ml aus dem graduierten Vorratsfläschchen des Strahlenschutzwagens Dadurch wird die Inkorporation des Radiojods in der Schilddrüse blockiert und seine Ausscheidung aus dem Körper beschleunigt

Spritzer radioaktiver Flüssigkeiten an nicht absorbierender Schutzkleidung können mit Zellstoff abgewischt und danach wie üblich dekontaminiert werden (Zählrohrmonitor gebrauchen vergleiche hierzu Tabellen 2 und 3 auch Ref 6)

Sind die beschriebenen Hilfeleistungen an der betroffenen Person durchgeführt wendet man sich den Reinigungs und Dekontaminierungsarbeiten in dem verseuchten Labor zu Unter Verwendung von Ferngreifzangen und langen Tiegelzangen (besonders bei Gammastrahlern) beziehungsweise mit den dicken Gummihandschuhen (bei Betastrahlern) wird hierzu zunächst saugfähiges Packpapier dann Zellstoff genommen und nach Gebrauch in den Abfallbehalter des Strahlenschutzwagens geworfen Gleichzeitig sind dabei

**Tabelle 1**

*Halbwertszeiten Halbwertschichten und Dosiskonstanten verschiedener gammastrahlender Radioisotope (nach QUIMBY)*

| *Isotop* | *HWZ* | *HWS* cm Blei | Dosiskonstante r pro mC h bei 1 cm |
|---|---|---|---|
| Natrium 24 | 15$^{h}$ | 1 5 | 18 4 |
| Kalium 42 | 12 5$^{h}$ | 1 2 | 1 50 |
| *Chrom 51* | *28 8$^{d}$* | *0 2* | *0 4* |
| Mangan 52 | 5 8$^{d}$ | 1 0 | 19 0 |
| Eisen 59 | 45 0$^{d}$ | 1 1 | 6 55 |
| Kobalt 60 | 5 2 | 1 2 | 13 5 |
| Kupfer 64 | 12 8$^{h}$ | 0 4 | 1 1 |
| *Zink 65* | *245 0$^{d}$* | *1 0* | *2 7* |
| Brom 82 | 35 7$^{h}$ | 1 0 | 15 1 |
| Jod 131 | 8 0$^{d}$ | 0 3 | 2 18 |
| Caesium 137 | 30 0 | 0 5 | 3 2 |
| Gold 198 | 2 7$^{d}$ | 0 3 | 2 35 |

Scherben und ähnliches zu entfernen Bei schwachen $\alpha$ oder $\beta$ Strahlern können als Abfallbehalter auch große Papiertuten verwendet werden (Ref 5)

Zweckmäßigerweise wird die mit einem Monitor festgestellte verseuchte Aera mit Kreide bezeichnet, wobei es manchmal ratsam ist, auch Dosiswerte mit anzuschreiben um die Reinigungs und Dekontaminierungsarbeiten innerhalb der benachbarten Stellen zu erleichtern Dadurch wird auch bei *spielsweise verhindert daß eine zu große Fläche* aufgewischt und damit womöglich noch kontaminiert wird, weil sonst oftmals auf einmal die ganze Oberfläche naß ist und man nicht mehr weiß wo das eigentliche Verseuchungszentrum ist

Konzentrationen starkerer Betaaktivität, etwa mit Gefäßbruchstücken zusammengetragene radioaktive Substanz, läßt sich — wenn erforderlich zeigt der Ionisationskammermonitor an — leicht durch Kunststoffplatten völlig abschirmen (Bild 2) Besonders empfiehlt sich Plexiglas und durchsichtiges PVC in einer Dicke von etwa 10 mm Hingegen werden solcherart Anhäufungen gammastrahlender Isotope am besten hinter einigen schnell aufgestellten Bleiziegeln zusammengetragen Dabei ist möglichst großer Abstand zu halten, die langen Greifzangen zu benutzen und die Anzeige des Ionisationskammer Monitors zu beachten

*Es erscheint noch zweckmäßig* an dieser Stelle auch auf die Halbwertschichten und die Dosiskonstanten der Gammastrahler hinzuweisen deren Benutzung die Bestimmung von Abschirmungen resp Dosisleistungen erleichtert (Tabelle 1) Bei den hier interessierenden Strahlenschutzzwecken ist es allerdings günstiger, statt der Halbwertschicht die 'Zehntelwertschicht (Bild 3) zu

**Tabelle 2**

*Empfehlungen fur maximal zulassige außere Verunreinigungen in Laboratorien fur Radioisotope (nach GUSSEW)*

| | Verunreinigung (Zerfalle/min auf 150 cm² Flache) | | | |
|---|---|---|---|---|
| | Fur Alpha Strahler | | Fur Beta Strahler | |
| | Vor Dekontamination | Nach Dekontamination | Vor Dekontamination | Nach Dekontamination |
| Hande | 75 | ohne | 5 000 | ohne |
| Wasche oder Handtuch | 75 | ohne | 5 000 | ohne |
| Laborkleidung aus Baumwolle | 500 | 100 | 25 000 | 5 000 |
| Schutzkleidung aus Plastik | 500 | 200 | 25 000 | 10 000 |
| Schutzhandschuhe Außenseite | 500 | 100 | 25 000 | 5 000 |
| Überschuhe Außenseite | 500 | 200 | 25 000 | 5 000 |
| Arbeitstische Gegenstande | 500 | 200 | 25 000 | 5 000 |

benutzen deren Großen sofort wegen der hoheren Schwachung anwendbar sind

Vor dem Fortsetzen der nachsten Reinigungsarbeiten mussen die erwahnten großeren radioaktiven Abfallmengen in geeigneten Behaltnissen entfernt werden Zum Transportieren und Aufbewahren radioaktiver Abfalle haben sich Behalter mit herausnehmbaren Kunststoffeinsatzen bewahrt die gegen γ Strahler mit Blei und gegen β Strahler mit PVC abgeschirmt sind

Nach dem Aufnehmen der verschutteten radioaktiven Substanz beginnt die eigentliche Dekontamination die unter Verwendung beider Monitoren sehr sorgfaltig vorzunehmen ist Auch in großerer Entfernung vom Verseuchungszentrum ist zu messen Eine wirksame Methode zur Dekontamination von Fußboden Tischen usw, ist flussige Seife oder ein anderes starkes Reinigungsmittel uber die betroffene Flache zu gießen und dann mit einem langstieligen Mop aufzuwischen Dieser Vorgang ist im Bedarfsfalle zu wiederholen Wenn erforderlich kann auch noch mit Tragerlosung nachbehandelt werden Sollte auch diese Methode nicht zum Ziele fuhren schlagt MALLARD vor einen abziehbaren Kunststofflack uber die verseuchten Stellen zu streichen was ein Freiwerden radioaktiver Dampfe oder Staubes verhindert Die betreffenden Teile mussen dann spater ausgewechselt und wie fester Abfall behandelt werden

Leider geben die von der I C R P herausgegebenen Empfehlungen keine Angaben uber zulassige Oberflachenkontamination In den Tabellen 2 u 3 sind deshalb einige von anderer Seite angegebene Werte gebracht um die maximalen außeren Verunreinigungen zahlenmaßig darzustellen und die Handhabung der Monitoren zu erleichtern Dabei gilt Tabelle 3 (nach DUNSTER

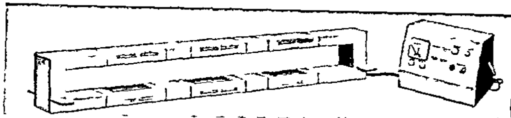


*Bild 4 Wasche Prufungsmonitor (mit frdl Genehmigung des Herstellers Technical Assoc Burbank California) Links Messrahmen rechts Anzeigegerat mit noch einer flexiblen Handsonde (Endfensterzahlrohr) Messbereich 0—2 000 Imp/min Ansprechzeit 2 bis 4 sec Empfindlichkeit um 0 15 μC (β)*

1955) fur ausgedehnte Flachenkontamination, also bereits fur schwierigere Falle, siehe Anmerkung daselbst Gleichzeitig sei an dieser Stelle auf die von der I A E O herausgegebenen Sicherheitsrichtlinien (Ref 6) hingewiesen Maximale Konzentrationen reiner Gammastrahler lassen sich unter Beachtung der Toleranzdosis *recht gut mit dem Ionisationskammer Monitor finden*

Die bei der Bestuckung des Strahlenschutzwagens erwahnten Gasmasken werden im Falle einer Verschuttung radioaktiven Pulvers (Staubschutz) oder radioaktiven Dampf erzeugender Flussigkeit (Gasschutz) gebraucht (MALLARD) Bei Radiojoddampf soll das Baumwollfilter der Gasmaske vorher mit *Natriumthiosulfatlosung getrankt* werden und *wenigstens etwas* wieder getrocknet sein, denn dann werden etwa 80 % des durchgehenden Radiojoddampfes absorbiert In einem richtig eingerichteten Laboratorium fur Radioisotope (SCHANZE 1957) werden aber alle Arbeiten mit solchen Stoffen mindestens in einem Abzug (der bei einem Zwischenfall einfach geschlossen wird) oder besser in einer 'glove box (*SCHANZE 1959 GRAUL 1958*) ausgefuhrt

Ein bei allen diesen Betrachtungen wichtiger Faktor ist die *physikalische* Halbwertszeit So genugt bei kurzlebigen Radioisotopen wie etwa $^{131}J$ $^{32}P$ $^{24}Na$ die Aufbewahrung kontaminierter Gegenstande in geeigneten Behaltnissen uber einige *Halbwertszeiten, um die gewunschte Aktivitatsreduktion* durch Abklingen herbeizufuhren Auch bei der Lagerung radioaktiver Abfalle ist dieses von Bedeutung

Zur *Dekontamination von Gerat* hat sich folgende Mischung bewahrt 3 Volumteile 10 % ige $HNO_3$ werden *mit 1 Volumteil* $C_2H_5OH$ vermischt und etwas 'Pril (Netzmittel) zugesetzt Naturlich gelten die im Zusammenhang mit dem Vorgehen nach Unfallen mit radioaktiver Substanz *gemachten* Dekontaminierungshinweise auch fur allgemeine, also nicht unfallgebundene Reinigungsarbeiten Den Detergentien kommt jedenfalls bei der gesamten *Dekontaminierung besondere Bedeutung zu* Speziell bei hartnackigen oder kritischen Fallen (etwa nach in Bleikammern zerbrochenen Becherzahlrohren) wird

**Tabelle 3**

*Empfehlungen für maximal zulässige Flächenkontamination (nach DUNSTER)*

| | |
|---|---|
| $10^{-5}\mu C/cm^2$ | für die Alphastrahler Po210 Ra226 Ac227 Pu239 |
| $10^{-4}\mu C/cm^2$ | für alle anderen Alphastrahler |
| $4 \times 10^{-4}\mu C/cm^2$ | für alle Betastrahler |

(An begrenzten Flächen bis 100 cm² pro m² können die angegebenen Werte um den Faktor 10 vergrößert werden Dieses gilt jedoch nicht für Kleidung oder für Gegenstände die irgendwie mit dem Munde in Berührung kommen können )

sowohl Titandioxyd mit verdünnter HCL als auch Siliziumchlorid zur Gerätedekontamination empfohlen Die Kombination der beiden Mittel soll besonders wirksam sein Auch sei an dieser Stelle auf die von der I A E O herausgegebenen Ausführungen (Ref 6) hingewiesen

Da eine Dekontaminierung von Geräten in Isotopenlabors wiederholt und regelmäßig erforderlich ist empfiehlt es sich diese Arbeiten immer an bestimmter Stelle (Spüle) vorzunehmen In vielen Fällen ist hierzu auch eine besondere glove box geeignet Für größere Isotopenlabors wird am besten eine sogenannte Dekontaminierungskammer dafür bereitgestellt

Um den Strahlenschutzwagen und seine Einrichtung jederzeit wieder einsatzbereit zu haben, ist es erforderlich, nach Inanspruchnahme verbrauchte Bestandteile und Lösungen zu ergänzen Schalen Abfallbehälter Zangen usw zu entleeren zu reinigen zu dekontaminieren und zum neuen Gebrauch wieder herzurichten Einzelne Bestandteile sollten dem Strahlenschutzwagen nicht entnommen werden um ihn immer einsatzbereit und komplett zu haben

*Behandlung und Umgang mit radioaktiver Wäsche* Es erscheint erforderlich zu diesem bisher nur wenig behandeltem Thema einiges zu sagen weil dieses für die Laboratoriumskleidung und für das Bettzeug vieler radiologischer Kliniken von Bedeutung ist und auch eine Dekontaminierungsfrage darstellt

Eine Schwierigkeit taucht zunächst auf nämlich zu entscheiden ob und welche Wäschestücke in die normale Wäscherei gegeben werden können und welche besonders dekontaminiert beziehungsweise extra gewaschen werden müssen Radioaktiv gewordene Wäsche kann nach DUNSTER immer dann mit der gewöhnlichen Schmutzwäsche zusammen gewaschen werden wenn feststeht daß einmal die Kontamination durch den normalen Waschprozeß sicher beseitigt wird und zum anderen die Aktivitäten ziemlich niedrig sind Auch die Gefährlichkeit (Radiotoxidizität) des kontaminierenden Radioisotopes (Ref 6 u SCHANZE 1957) und die Art seiner chemischen Verbindung

spielen dabei eine Rolle. So können z. B. $^{32}P$-Verunreinigungen schwer entfernbar sein, wenn sich unlösliche Phosphate bilden.

Sorgfalt und Kenntnis erfordert auch das Prüfen der Wäschestücke vor dem Waschen mit dem Monitor (Endfensterzählrohr benutzen), sowie das Handhaben und Sortieren. Dabei sind immer Gummihandschuhe, bei Gammastrahlern noch lange Tiegelzangen zu benutzen. Bei schweren Gammaverseuchungen, z. B. Unfallwäsche, kann Bleigummischutz für Hände und Körper — wie im Röntgenwesen gebräuchlich — trotz der hohen Gammaenergien diskutabel sein. Die Möglichkeit einer äußeren Strahleneinwirkung und ein Inhalationsrisiko sind wohl meistens vorhanden. Zweckmäßig sind zum Sortieren mit PVC bedeckte Tische, deren Rand hochgezogen ist. Auch können bei starker Betaverseuchung, z. B. Unfallwäsche, Schutzschilde aus transparentem Kunststoff nützlich werden.

Unkompliziert wird nach DUNSTER das ganze Problem, wenn die meisten Wäschestücke mit nicht mehr als $10^{-3}\,\mu C/cm^2$ an Betastrahlern kontaminiert sind, auch wenn einige Stücke das zehnfache dieses genannten Wertes aufweisen, denn die Dekontamination von β-Aktivitäten dieser Größenordnung in der normalen Wäscherei bringt keine Komplikationen mit sich. Dennoch wird es sich auch bei diesen geringen Aktivitäten überall dort lohnen, wo relativ viel solche Wäsche anfällt, eine besondere separate Waschanlage in einem eigenen Raum einzurichten.

Eine solche 'aktive Wäscherei' wird am besten dem Laboratoriumstrakt oder der Bettenstation angeschlossen und für größere Aktivitäten ausgelegt. Zu ihrer Haupteinrichtung gehören: Waschmaschine (gute Haushalts- oder Industriewaschmaschine), Schleuder (auch in Kombination möglich), sowie je ein besonderer Tisch für die Handhabung kontaminierter und gewaschener Wäsche. Die Benutzung einer separaten Waschanlage gilt grundsätzlich für alle größeren Isotopenlabors und Kliniken, in denen offene Radioisotope in größerem Umfang appliziert werden. Überhaupt muß Wäsche, die höhere Aktivitäten als oben genannt, respektive Alpha- oder Gammastrahler in sich aufgenommen hat, extra gewaschen werden.

Zu berücksichtigen ist weiterhin, daß das Waschen kontaminierter Wäsche einen sekundären radioaktiven Flüssigkeitsstrom aus der Waschlauge und dem Spülwasser erzeugt, der deshalb der Anlage zur Beseitigung radioaktiver Abwässer zugeführt werden muß. Für orientierende Messungen kann es auch empfehlenswert sein, zur Beobachtung der Waschwasseraktivität der Waschmaschine ein kleines Misch- und Meßgefäß (am besten aus PVC) mit Tauchmeßsonde (SCHANZE 1959 u. 1961).

Nach dem Trocknen der dekontaminierten Wäsche ist sie vor dem Verlassen der 'aktiven Wäscherei' sorgfältig mit einem Monitor zu prüfen, ob eventuell noch Restaktivität zurückgeblieben ist. Dazu ist bei größeren Wäschemengen und bei Bettzeug ein besonderer Wäsche-Prüfungsmonitor zeitsparend und zweckmäßig. Bei einem solchen, in Bild 4 gezeigtem Gerät wird die

Wäsche durch den Meßrahmen (Innenmaße 10 × 100 cm) geführt, wo sie *von sechs gegen Umgebungsstrahlung abgeschirmten dünnwandigen* Zählrohren von oben und unten abgetastet wird. Beim Vorhandensein einer Restkontamination, die größer ist als der am Anzeigegerät vorgewählte Wert, wird noch ein akustisches und optisches Signal gegeben. Weiterhin ist noch eine Handsonde zum Zwecke der genauen Lokalisation einer festgestellten Kontamination am Anzeigegerät angeschlossen.

Zeigt sich nach dieser Schlußprüfung noch Kontamination, so ist der Waschvorgang, für den übrigens normale Waschmittel verwendet werden, zu wiederholen.

## ZUSAMMENFASSUNG

Ein Strahlenschutzwagen wird beschrieben, der alle Dinge, die bei einem Unfall mit offenen radioaktiven Stoffen in Isotopenlaboratorien benötigt werden, enthält. Anleitungen zur Dekontamination und zum Vorgehen nach einem Unfall mit Radioisotopen werden auch gegeben. Weiterhin wird die Behandlung radioaktiver Wäsche erläutert und eine aktive Wäscherei beschrieben.

## SUMMARY

An accident trolley is described that contains everything needed if an accident with radioactive materials occurs. Instructions for decontamination are given and measures to be taken after mishaps with open isotopes are recommended. Cleansing and treatment of laundry that has been contaminated with radioactive material are discussed and an active laundry is described.

## RÉSUMÉ

Description d'une voiture de secours contenant tout le matériel nécessaire en cas d'accident libérant des substances radioactives. L'auteur donne des indications pour la décontamination et recommande les mesures à prendre après les accidents libérant des isotopes. Il explique comment traiter le linge radioactif et décrit une blanchisserie active.

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